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DERMATOLOGY FOCUS™

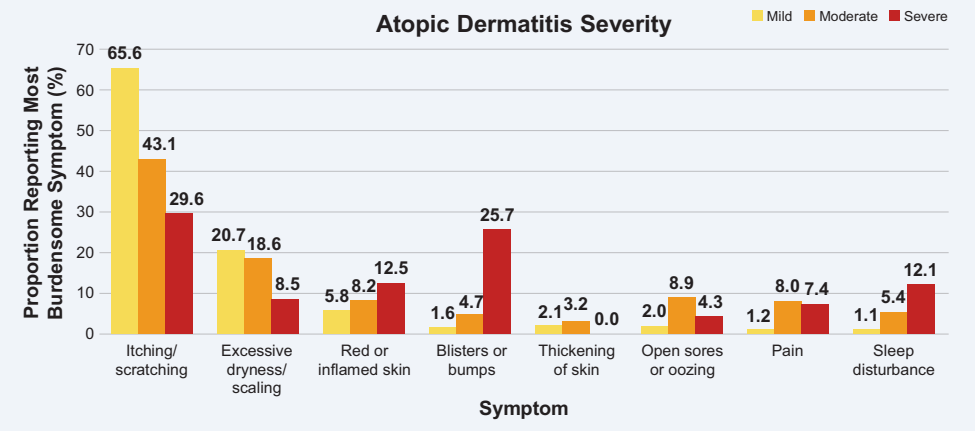
DF *Also In This Issue*

Former DF Awardee, Jonathan I. Silverberg, MD, PhD, MPH, Advances Care for AD

2020: $2.71 Million Granted in DF Research Funding

Understanding and Treating AD in the Real World

Atopic dermatitis (AD)—a high-impact relapsing inflammatory skin condition with immune dysfunction involving both lesional and nonlesional skin—is characterized by prominent pruritus, eczematous lesions, excoriations, lichenification, crusting and oozing, dry skin, and skin pain. It affects as many as 13% of children and adolescents and 7% of adults in the U.S. Treatment options are finally beginning to advance due to recent identification of major immune signaling pathways in AD, which initiated the development of targeted biologic drugs. (Dupilumab, the first, was FDA approved in March 2017.) Frustratingly, however, this long-awaited therapeutic leap forward has turned out to be only the start to achieving the elusive goal of restoring patients' lives—and psyches—to normal. This common skin disease is increasingly recognized now as profoundly more complex and heterogeneous, substantially more debilitating, and far more challenging to assess than has been realized. These deficits in knowledge have significantly impeded patient care, with the result that many with AD are either undertreated, or not receiving treatment at all. The burdens on their health and quality of life (QOL) are severe.



Itch and AD symptom burden. The symptoms identified as the most burdensome by a population-based cross-sectional sample of adult patients were stratified by self-reported global AD severity. *Itching/scratching* was paramount at all levels. (Reprinted with permission from JI Silverberg et al., *Ann Allergy Asthma Immunol.* 2018;121:340–47.)

Fortunately, clarity has begun to emerge, in large part through the probing research of AD specialist Jonathan I. Silverberg,* MD, PhD, MPH. Silverberg is now Associate Professor of Dermatology and Director of Clinical Research and Contact Dermatitis at The George Washington University School of Medicine and Health Sciences. This was preceded by six years at Northwestern Medicine, where he had been Associate Professor of Dermatology, Medical Social Sciences, and Preventive Medicine. He had established the Multidisciplinary Eczema Center there to provide uniquely comprehensive and coordinated care for challenging adult patients. He was also director of the patch testing clinic at Northwestern Memorial Hospital. (He is now Adjunct Associate Professor at Northwestern.)

Silverberg has devoted his research agenda to filling in the extensive real-world knowledge gaps about AD. This includes identifying and characterizing the spectrum of significant health issues that are closely associated with or actually part of AD; profiling the unexpectedly diverse and concerning effects on patients' lives; and developing tools for adequately assessing AD's manifestations, severity, and impact, especially with utility in the clinical setting. Silverberg's perception and dedication, along with the advent of comprehensive databases and the unique data pool that he created with the patient registry he established at the Multidisciplinary Eczema Center, have enabled him to cover extensive and varied ground in a short period of time. He has been redefining the nature, complexity, heterogeneity, and impact of AD, and thus providing essential aid and perspective for both clinicians and trialists.

Discovering His Path

Silverberg knew early on that he would become a physician-scientist,

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Landmark Progress in Patient Care Began With DF Award

Jonathan I. Silverberg, MD, PhD, MPH

Each year, the Dermatology Foundation carefully identifies emerging investigators whose ideas have the potential to significantly further patient care, and who possess the abilities to make this happen. In 2015, Dr. Silverberg was one of these young investigators. This small investment in progress has already produced substantial clinical advances. The 3-year Career Development Award in Health Care Policy/Public Health that Dr. Silverberg received to study racial and ethnic healthcare disparities in atopic dermatitis (AD) enabled him to launch a powerful, multipronged patient-oriented research agenda that has been generating fundamental progress in the understanding and care of AD patients. He has illuminated the systemic nature and severe multifactorial burden of AD, documented adult-onset disease, and accurately assessed the multiple components of patient status. Clinicians have already gained substantial tools for helping their patients eliminate the severe burdens of this chronic inflammatory skin disease—and there is more to come.

Jonathan Silverberg's passion for bringing better care to AD patients began when he chose to study its epidemiology for his MPH thesis. AD had initially been a topic of convenience, but he became intrigued as he discovered its remarkable heterogeneity and identified extensive gaps in both knowledge and practice. After completing his dermatology residency in 2013, Dr. Silverberg joined the department of dermatology at Northwestern Medicine and established the Multidisciplinary Eczema Center. Although his research there began with population studies, in line with his epidemiology training, his clinical exposure to the spectrum of challenging AD patients opened his eyes to the critical need for patient-centered research. This is where his DF Career Development Award made the critical difference—for him as an investigator, and for patients with this common and potentially debilitating chronic skin disease.

Dr. Silverberg explains that this award "enabled me to establish an ongoing database from the patients seen at the Eczema Center, and gave me the protected time essential for collecting and exploring the resulting data. The funding allowed us to phenotype the disease characteristics and burden for each patient, longitudinally follow them—and then study and understand which outcome measures perform best, identify the best predictors of long-term health outcomes, etc. By supporting this," Dr. Silverberg adds, "the DF award allowed me to completely pivot in my research, from the population level to the bedside." The clinical registry is enormous and of inestimable value, and Dr. Silverberg's results have been transformational for patients with moderate to severe disease.

In addition, Dr. Silverberg has won numerous teaching awards and was recently honored by the AAD as a Patient Care Hero. He is a founding member of RAD—Revolutionizing Atopic Dermatitis—devoted to educating dermatologists, a spectrum of other health professionals, and patients. He has also published prolifically, and holds several editorial positions.

Dr. Silverberg—now at George Washington University—continues to transform physicians' ability to help their AD patients. He ties this exceptional clinical progress directly to his "invaluable DF research funding."

but did not want to follow in the specialty footsteps of either his father or older sister—endocrinology and pediatric dermatology, respectively. He set his sights on neuroimmunology, and during medical school at SUNY-Downstate, he completed his PhD and then an MPH in biostatistics and epidemiology to gain strong translational and clinical research skills. Silverberg's doctoral research experience, though, had led him to realize that neurology did not appeal to him in either the lab or the clinic, but immunology—especially allergy—truly did. And this launched his circuitous path to discovering his perfect fit with dermatology.

For his MPH research, Silverberg wanted to study a highly prevalent allergic disease, but one involving a clinical diagnosis to avoid time-consuming objective testing. He selected AD—still considered an allergic disease by some then—because it met both requirements. "Then during my research, I became totally infatuated with it. I began to discover so many knowledge gaps, so many practice gaps, so many fascinating aspects of this disease with respect to its heterogeneity—how it presents, the range of triggers, the different risk factors, the different protective factors," he recalls. "And before long—I was hooked!" Silverberg was still unsure about dermatology, "but when I finally began my elective—I knew!" His residency at St. Luke's-Roosevelt in New York connected him with Vincent A. DeLeo, MD, the mentor who stimulated his interest in contact dermatitis. "Once I began to see the relationship between that and AD, my direction was clear."

Silverberg's experiences with the AD patients he saw there were also formative, as they inspired the unique way in which he practices. His dialogue with these patients began to open his eyes to the extensive burden they were living with, and it became clear to him that the proper management of all of the direct and indirect effects of AD often requires expertise beyond the scope of typical residency training. Silverberg developed his concept of the Multidisciplinary Eczema Center for challenging AD patients that he would establish at Northwestern, bringing together dermatology, allergy and immunology, neurology, psychology, and sleep medicine, and staffed with specialized nurses. And this unique AD resource would, in turn, become his gold mine for research ideas and data.

Inspiration and Focus

"Most of the research questions I ask now are the result of my unusual clinic setting, which allows me to spend 30–60 minutes with each new patient," Silverberg explains. "Having this time to talk with my patients to improve my understanding of their individual skin disease revealed a massive patient burden. So I began to study these associations with AD, and quickly recognized a whole world of previously unrecognized symptoms and comorbid health disorders. This really refocused me, and I made a complete pivot," he continues. "I took my research from the population level down to the bedside, because I realized the urgent need to really understand the more clinical risk factors and the global patient-burden of disease."

Silverberg explains that the overarching theme of his contributions "is trying to improve our understanding of AD in the real world and how to properly assess it." Central to this is accurately characterizing and quantifying the burden of disease. "It is so much more extensive than we had imagined—for both adults and children—that we now consider AD to be a systemic disorder with a multi-organ burden," Silverberg emphasizes.

His research already provides the ability to improve current clinical care significantly (see box on page 10). As he continues, the benefits will ultimately enable matching new and emerging treatments with the appropriate patients. "If we don't *really* understand the fundamentals," he stresses, "we can't fully and effectively understand this disease in the real world and how properly to assess it. And without that, we will never be able to get the new medications—those available and those on the horizon—to the right patients."

What's In a Word?

AD is a disease that can be traced back to ancient Egypt, but because it has been regarded as essentially a disease of childhood, its true prevalence had not been recognized and its potential impact on the lives of adult patients was not on the radar. The barriers to identifying patients and developing an accurate body of knowledge have been amplified by the highly unsystematic terminology.

Silverberg knew that lack of a standardized nomenclature for AD interferes with scientific communication, but not until an instructive encounter in the clinic did he realize that the concurrent use of *atopic dermatitis* and *eczema* creates serious confusion among patients and providers. "When I told this particular patient that he has atopic dermatitis," Silverberg

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Please address correspondence to:
Editors-in-Chief, Dermatology Focus
c/o The Dermatology Foundation
1560 Sherman Avenue, Suite 500, Evanston, Illinois 60201
Tel: 847-328-2256 Fax: 847-328-0509
e-mail: dfgen@dermatologyfoundation.org

Published for the Dermatology Foundation by
Robert B. Goetz—Designer, Production
Sheila Sperber Haas, PhD—Managing Editor, Writer

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DF President Dr. Janet A. Fairley: *Announced 2020 Research Awards*

For the first time in the Dermatology Foundation's 55-year history, the Annual Meeting of Membership, and other key events, could not take place in person. The COVID-19 pandemic had suddenly created a public health emergency that curtailed travel. Despite this profound disruption, the DF—like many organizations—established the capability to carry out all essential functions virtually. This included the thorough interactive review and ranking of DF research award proposals, and Board approval of 2020 funding. Dr. Fairley shared her inaugural report on the year's progress in writing.

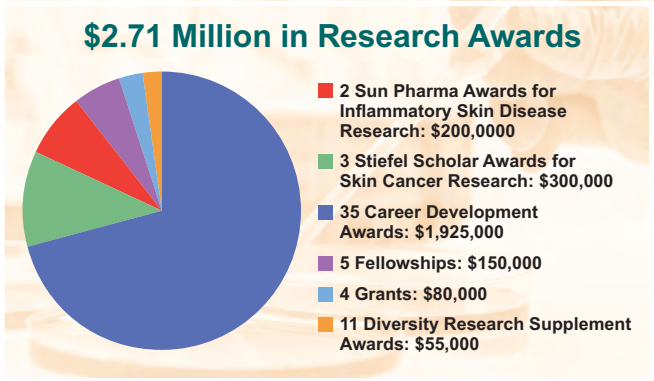
"I hope you are all safe and well during a very difficult personal and professional time," Dr. Fairley began. "And I thank all of you for your continued commitment to the Foundation. Your contributions made it possible to fulfill our mission again this year—to fund promising research that will enable advancements in patient care. The DF and our newest award recipients are fortunate to have your support."

Solid Support Advances Patient Care

"Individual membership contributions for 2019 showed an increase of 3.2% over the previous year," Dr. Fairley noted. "Many thanks to our numerous volunteers who worked to make our results as positive as possible, and a special thank you to all of our colleagues—both those who renewed their commitment to the work of the DF this past year, and our new members."

The Foundation is pleased to recognize the generosity of the many members who increased their level of giving this past year. The *Annenberg Circle* welcomed 17 new members who raised their commitment to the DF to $25,000. *AC Sustaining* recognized 18 members who have chosen either to give an additional annual $5,000 a year or have extended this initial pledge for multiple years. *Leaders Society* enjoys 96 new members contributing $1,500 annually. Dr. Fairley praised the Visionary Society, the DF's planned giving program. "I am deeply grateful to each of the five new Founding Members who have added the DF to their estate plan."

Dr. Fairley formally thanked the Corporate Honor Society, the DF's most generous corporate supporters, led by the Platinum Benefactors, each of whom contributed $200,000 or more last year: Galderma Laboratories, L.P., Sun Dermatology, and Unilever. She extended "a special thank-you to the American Academy of Dermatology and to the Women's Dermatologic Society for their individual contributions of $55,000 to help make possible the work of this year's research award recipients."



2020 Research Awards

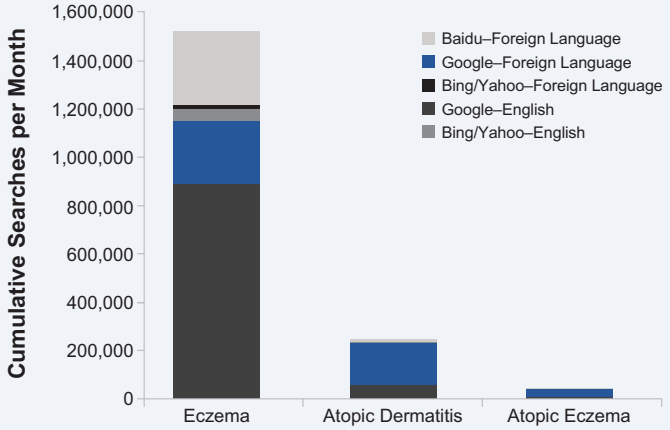
"Although all DF meetings in Denver had to be canceled at the last minute, we were extremely fortunate during this unprecedented and hectic new reality to maintain the dedicated commitment and time of our volunteer Medical and Scientific Committee and Panel. They adjusted to the sudden need to conduct the scientific review of our award applications virtually. We are thankful to each Committee and Panel member, and to Committee chair Jonathan H. Zippin, MD, PhD, and Panel chair Anna L. Bruckner, MD." The enormously gratifying result was the funding of 60 promising research projects/investigators in 16 award categories. "On behalf of all DF officers and Trustees, I extend my deep appreciation to all of our members and other constituents for making these results possible."

Present and Future

Dr. Fairley closed with an important message. "Although we are all operating in new territory now and do not know what the future will bring, *we know that there will always be patients who need our help. If we continue to work together, we will be able to add significantly to the tools and treatments available to dermatologists everywhere.*"

recalls, "he said: 'No. I've been told I don't have that, that I have eczema.' And I realized that patients who are misled by the language do not understand what they have—and thus cannot be empowered to manage their disease and take responsibility for the cumbersome topical regimens and avoiding their triggers."

Eczema—from the Greek word for "boiling"—entered the medical literature in the late 18th century as a clinical description of the primary lesions. *Atopic dermatitis*—introduced in 1933—names the disease and etiology. Hanifin's and Rajka's gold standard diagnostic criteria were published in 1980. Silverberg knew that controversy over the ideal nomenclature persisted, but he had no idea to what extent. His research uncovered opposing patterns. In the scientific literature, *AD* had become the dominant term, although never completely replacing *eczema* and *atopic eczema (AE)*. But in internet searches from 2014–2016, *eczema* was the hands-down winner with 84% of the monthly searches across a number of languages (see graph at right). *AD* accounted for only 14%, and *AE* for just 2%. English-language searches were even more lopsided: 93% using *eczema* and 6% using *AD*. Silverberg emphasizes the critical need for standardized nomenclature across clinical practice, the research community, and patient health literacy—and that it should be AD with the precision it provides.



***Eczema* robustly predominates in web searches.** Global data for the average monthly searches from 2014–2016 for *eczema* vs *AD* vs *atopic eczema* covered Google, Bing/Yahoo, and Baidu and included 38 languages. *Eczema* won hands down, ranging from 81% in Google to 91% in Bing/Yahoo and 96% in Baidu. (Reprinted from Shuai Xu, et al., *Dermatitis.* 2017;28:276–79, with permission from Wolters Kluwer Health, Inc.)

Age of Onset—It's *Not* Just Children

A major barrier to accurate observation and fruitful research had been the misconception that AD is a pediatric disease. The typical epidemiologic study did not even include adult patients. Silverberg's clinical experience clearly contradicted this, and he wanted to get a sense of the real distribution. Published observational studies that analyzed the age of AD onset beyond 10 years of age provided 17 studies for a meta-analysis, and the proportion of adult-onset AD—26.1%—was considerably higher than he had speculated. Consistent phenotypic differences included higher proportions of foot dermatitis and lower proportions of flexural eczema in adult-onset patients. These clinical characteristics might make adult-onset AD difficult to distinguish from other entities that commonly begin in adulthood, eg, allergic contact dermatitis and cutaneous T-cell lymphoma, which have to be ruled out.

Symptoms: So Much More

AD is a highly symptomatic disease, but for many years itch had been the sole symptom recognized. In addition to enhancing the understanding of itch and its burden in adults, Silverberg has also significantly expanded the list of symptoms, establishing the presence—and added burden—of sleep disturbance, mental health issues (anxiety, depression, and suicidality), skin pain, and cognitive dysfunction. And he has developed several valid, easy-to-use patient-response symptom assessment tools appropriate for both clinical and trial use.

Itch

The itch associated with AD is the most common and most burdensome symptom of this inflammatory skin disease (see graph on front cover). Silverberg's awareness of the particularly heavy burden that itch creates for a subset of AD patients came from following up with several patients who had missed their clinic appointments. He learned that one had been hit by a bus, another had fallen down the stairs, and the third had been in a car accident. "This patient connected the dots for me," Silverberg says. "It had to be more than coincidence that all three had been injured in accidents. I asked if this was her first car accident. 'No—it was my third! When I leave work to drive home, I'm so unbearably itchy that I strip down in my car and scratch while I drive. Sometimes the itching is so distracting that I've gotten into an accident.'" Silverberg and his group carried out several studies, learning that there is a subgroup of patients at high risk for being so overwhelmed by itching that it impairs their safety. Antihistamine-caused sedation and fatigue from sleep deprivation can exacerbate this. Thus it is critical to identify these patients.

Silverberg recognized that itch in AD is complex, with substantial variability in intensity, in frequency, and in the phenomena that trigger it. Because not a single one of its numerous triggers—which include heat, sweat, dryness, clothing, and stress—affects all patients, he sought a better understanding of trigger patterns in adult patients. Which ones are most common, what are their predictors, and are there any associations with AD severity and clinical course?

Before he and his team could explore this, however, they needed a reliable way to assess patients' itch realities. In the absence of universally accepted biomarkers or objective measures of itch, "patient-reported outcomes (PROs) are an ideal approach for measuring itch," Silverberg has stated. But many different PRO approaches were being used, with no standardization. He knew the outstanding capabilities of PROMIS (see box on page 6), which included a segment addressing itch. "But not all itchy diseases are created equal," Silverberg points out, so he and his colleagues developed additional components—numeric rating scales, verbal rating scales, and frequency assessments—specifically addressing itch in the context of AD and added them to PIQ, the PROMIS Itch Questionnaire, to create PIQ-Itch. It was simple to use, took patients roughly 1 minute to complete, did an excellent job of assessing an AD patient's itch and its impact, and was feasible for use in clinical practice and clinical trials.

Patients at the Multidisciplinary Eczema Clinic (n=587) each answered the PIQ-Itch and a variety of other self-report

questionnaires that included itch and/or AD severity, and a dermatologist provided a severity assessment. 65% of this group reported ≥1 itch trigger in the preceding week, and 36% had ≥3 triggers. The most common were stress (35%), sweat (31%), weather change (25%), dry air (24%), and heat (24%). Increasing number of itch triggers was associated with increasingly severe disease, and most patients with ≥3 triggers reported ≤3 months per year of remission, ≥2 flares per year, and seasonal worsening of their AD. Allied research pointed to sweat, dryness, and stress as the triggers requiring the greatest attention by clinicians. The avoidance challenge posed by multiple itch triggers suggests benefit from stepping up therapy earlier than for patients with more manageable triggers.

Sleep Disturbance

Silverberg's first study of sleep dysfunction with adult AD patients was an attempt to gain basic information. The general premise that fragmented sleep and fatigue in adults are associated with poor health outcomes was well known, and although he observed this in his patients, the specific picture in AD had not been defined. Using the 2012 National Health Interview Survey, a cross-sectional questionnaire of 34,613 adults, Silverberg found AD associated with higher odds of fatigue, regular daytime sleepiness, and insomnia, and that patients experiencing AD plus these sleep symptoms—as opposed to AD or sleep symptoms alone—had significantly higher odds of poorer health-related outcomes. To characterize the patient burden, Silverberg and his team used a nationally representative sample of 5,563 adults from the 2005–2006 NHANES database to conduct another questionnaire-based survey. AD was associated with significantly higher odds of sleep disturbances, feeling unrested, and fatigue affecting numerous daily activities and sometimes the ability to work.

Next, Silverberg wanted to do a prospective study of adult AD patients, but patient-reported outcome measurement tools targeting sleep disturbance and its impact in AD patients had not been validated, and the general assessment tools including these sleep issues had not been validated for AD patients. Silverberg remedied this. He assessed POEM-sleep and SCORAD-sleep, created for AD patients. He evaluated the general questionnaires 5D-sleep, ItchyQOL-sleep, and the two 8-item sleep-oriented PROMIS questionnaires. PROMIS SD (sleep disturbances) assesses sleep over the past week. PROMIS SRI (sleep-related impairment) is an overview of sleep-related functional impairments, and feasible for clinical practice. Silverberg chose the two PROMIS questionnaires for his next investigation.

Silverberg and his coworkers suspected that most patients experience sleep disturbances and related impairment, but that only a small patient subset—defined by both severe AD and severe itch—experiences them profoundly. This was validated when the PROMIS SD and SRI questionnaires were filled out by 287 patients belonging to the National Eczema Association or National Eczema Society. SD and SRI occurred even in mild AD, but were most common in severe disease.

Silverberg explains that patients with severe disease often feel inundated by their symptoms, which results in significantly disturbed sleep. In addition, poor sleep efficiency and duration also result directly from itch, scratching, and skin pain. Poor

(Continued on page 8)

The ABCs of AD Tests

A burgeoning number of tests—some broad, some highly focused—are available now for attempting to determine objective disease severity, the patient's perception of severity, what this is based on, the aspects of life that are affected, the severity of specific high-burden symptoms, the nature of these burdens, and overall quality of life. Many are designed for clinical trials, but some test developers have come to recognize the critical value of tests in clinical practice—especially *patient-reported outcome (PRO)* measures—to assess a patient's status at baseline and then during an intervention. To be integrated into clinical practice, they must be easy and rapid for the patient to answer and for the clinician to score and interpret. Below are AD-specific and general instruments that Silverberg has validated for AD.

AD-Specific

Patient-reported global AD severity: mild, moderate, severe.

EASI (Eczema Area and Severity Index): clinician-reported; signs on 4 body sites.

POEM (Patient-Oriented Eczema Measure): assesses severity via the frequency of the 7 most relevant symptoms. HOME (Harmonising Outcome Measures for Eczema) chose it as the core assessment instrument.

SCORAD (Scoring Atopic Dermatitis): 6 signs on 8 body sites, pruritus, sleeplessness. Variants: oSCORAD (Objective SCORAD); PO-SCORAD (Patient-Oriented SCORAD); PO-SCORAD-itch; PO-SCORAD-sleep.

General

DLQI (Dermatology Life Quality Index): 10-item questionnaire for dermatologic diseases in general; the most frequently used QOL instrument in AD studies.

ItchyQoL (Itchy Quality of Life): 22 questions for patients with chronic pruritus covering symptoms, physical functioning, emotions.

SF-12 (Short Form-12): mental and physical health scores not specific to skin disease, but capturing many QOL domains affected by AD.

PROMIS (Patient-Reported Outcomes Measurement Information System): supported by the NIH, it consists of validated item banks and questionnaires measuring key health-related outcome domains manifested in a variety of chronic diseases. Silverberg validated the sleep-related questionnaires, PROMIS SD and PROMIS SRI, for adults with AD, and developed PIQ-Itch for itch severity assessment.

2020 Research Award Proposals

Jonathan H. Zippin, MD, PhD, Led Review Session

Dr. Zippin, Vice Chair of Research and Associate Professor of Dermatology at Weill Cornell Medicine, chaired the DF Medical & Scientific Committee's virtual review of proposals submitted for funding in 2020. These responsibilities followed two years as a Committee member. Dr. Zippin appreciated the opportunity to shepherd this selection process because of its critical role in enabling progress in understanding and treating skin diseases.

"The Dermatology Foundation is an essential source of funding for young investigators at critical times," he explains. "It has enabled a great many investigators—whether they are in the clinical, basic science, or translational research space—to continue their research. Because of this early support, so many of the existing advances in dermatologic science and care owe a debt to the DF."

Dr. Zippin himself is an example. His two DF research awards were "essential" to his progress in skin biology and patient care because they enabled his transition "from finishing my post-doc work to applying for NIH funding," thus enabling him to improve the understanding and treatment of skin diseases. Following this path, Dr. Zippin established and directs the Contact, Occupational, and Photodermatitis Service at Weill Cornell, and serves as the Vice Chair of Research in the department. He is also Associate Professor of Pharmacology and a member of the Englander Institute for Precision Medicine and the Meyer Cancer Center. Both his molecular and translational research evolved from his "dedication to understanding the role of cyclic AMP signaling in skin disease." His work has revealed new biology now enabling productive insights inato chronic inflammatory diseases, melanoma, and pigmentation, and some of the research tools Dr. Zippin and his lab developed have been converted to diagnostic and therapeutic applications. He is currently exploring a newly discovered mechanism that controls pigmentation and melanoma, and has recently developed a new approach to inhibiting T cells. He is currently characterizing novel small molecules as an alternative to steroids for treating inflammatory skin diseases and as an innovative approach to treating diseases of pigmentation.

Dr. Zippin—who brought this enthusiasm along with extensive grant application review experience to the 2020 applications for DF funding—described his goal as ensuring "that all proposals were evaluated fairly, and that those selected were held to standards of the highest quality."

Epidermolysis bullosa expert Anna L. Bruckner, MD, MSCS—Associate Professor of Dermatology and Pediatrics at the University of Colorado School of Medicine and Pediatric Dermatology Section Head at Children's Hospital Colorado—chaired the Committee's Clinical/Medical/Surgical/Dermatopathology Panel for her second year. (See her profile in *Dermatology Focus*, Fall/Winter 2018.)

The DF is especially grateful to the Committee and Panel members this year (see Winter 2019/2020 for rosters). They responded with dedication and flexibility to the sudden need to replace the intensive in-person proposal review process with a virtual meeting, well before the virtual experience had become a familiar format.

Dr. Zippin received a 3-year DF Physician Scientist Career Development Award in 2010 to study the role of soluble adenylyl cyclase in psoriasis pathogenesis. In 2012, he received a Research Grant to study the role of soluble adenylyl cyclase in IL-22-dependent signaling in keratinocytes.

Support the DF *Advance All of Dermatology*

Despite these uncertain times, the Foundation's Research Awards Program must continue to further progress in clinical care. It has become the primary force launching the research that transforms our understanding of skin biology, disease pathology, and capabilities for patient care.

This year's award recipients began their work on July 1. Now we are working to ensure funds for deserving 2021 projects. On behalf of all of the patients whose lives will be improved through the progress initiated by DF-supported research, it is so important to become a DF member. (Visit *dermatologyfoundation.org/members/*)

Your patients are the ultimate beneficiaries. Progress in patient care will not happen without you.

DF Executive Director Sandra Rahn Benz Retires After 41 Years

Sandra Benz has been a steady guiding hand in the Dermatology Foundation's growth from a small organization with high hopes into a critical force in the specialty. When Ms. Benz began her tenure more than 40 years ago, the DF funded a handful of $5,000 research grants. Under her leadership, the DF awarded $78 million in research support to recipients who have spearheaded progress in skin biology and clinical care. She was also instrumental in creating the *Leaders Society* and the Annenberg Circle, which are now the primary foundation for physicians' individual investments in the future of the specialty.

DF President Janet A. Fairley, MD, expresses the Foundation's gratitude. **"For four decades, Sandra has done an extraordinary job of helping the DF grow into the premier organization it is today. We are all indebted to her for her strong stewardship, fundraising expertise, and ability to engage our members and many constituents for the benefit of the specialty. We wish her every happiness in retirement."** Ms. Benz shares: "It has been an honor to have contributed to the important work of the Foundation, and I am grateful to all those who have been so supportive of the DF, and of me personally, over the years."

sleep impacts daily activities, work productivity, mood, and mental health. Sleep disturbance has also been linked to injuries and fractures, including motor vehicle accidents and workplace injuries, and cardiovascular disorders. In the other direction, insufficient sleep can lead to increased inflammation and pain perception, which worsens itch, which then worsens sleep further. Sleep disturbance in AD is exceedingly complex, and the underlying mechanism remains to be clarified.

Silverberg cautions that sleep disturbances may be underdiagnosed in the adult AD population, and recommends routine screening for them in clinical practice. He finds that a multidisciplinary approach aimed at improving itch *and* AD severity *and* symptoms of allergic disease *and* mental health is needed to achieve good sleep outcomes.

Mental Health Issues

Mental health issues have not conventionally been included among AD symptoms, and when they are recognized by the dermatologist, they are typically regarded as unrelated to the patient's AD. But Silverberg's immersive experience with challenging patients led him to recognize that anxiety, depression, and suicidality are actually AD symptoms, and that this intense psychological distress typically resolved once a patient's AD was tightly controlled. Previous studies addressing an association had produced conflicting results.

Silverberg began with the literature, a systematic review of published observational studies analyzing depression in AD followed by a meta-analysis. He found that patients with AD had a significantly higher prevalence of depression than those without, and that among all patients with depression, AD patients had significantly higher scores. Suicidality was more prevalent in patients with AD (12.2% vs 6.4%). Overall, 1 in 4 patients with AD had depressive symptoms, almost 1 in 6 had clinical depression, and 1 in 8 had suicidal ideation. Four studies also noted the significant improvement in mental health symptoms once the patient's AD was successfully treated.

Then Silverberg and his colleagues conducted a cross-sectional, population-based analysis of 2,893 adults in the Atopic Dermatitis in America survey, which in turn was sampled from the long-standing Growth from Knowledge Panel. Patients completed the Hospital Anxiety and Depression Scale (HADS-A for anxiety, HADS-D for depression) and self-assessment tools for their AD (see the box on page 6): self-reported global AD severity, POEM, and PO-SCORAD. AD patients had substantially higher HADS scores and more borderline and abnormal scores compared to non-AD adults, and had a much higher prevalence of self-reported healthcare-diagnosed anxiety or depression in the past year. All patients with severe AD reported anxiety and depression. One surprise was the substantial proportion of AD patients reporting borderline or abnormal mental health scores whose mental health issues had never been diagnosed.

"Taken together, it appears that AD—particularly moderate to severe AD—is associated with profound symptoms of anxiety and depression, and that AD severity is the major driver," Silverberg observes. "This supports the heavy mental health burden that AD places on patients, and reflects what I see clinically." And he adds that "it is important for clinicians to recognize that virtually all patients with moderate to severe AD have these symptoms. And the more severe forms of AD are a completely devastating disease with waves of depression and suicidality higher than almost all other chronic diseases." Silverberg strongly recommends incorporating assessment for mental health symptoms into standard practice, and suggests the HADS for this purpose.

Silverberg emphasizes that "because the anxiety and depression we see in these patients are actually symptoms of AD, I think of them now in the same way that I think of itch and pain. Getting really good control of their disease is key. When that happens, the anxiety and depression improve dramatically along with itch and skin pain." The presence of depression, anxiety, and suicidality are actually a clue that the patient's skin disease is more severe than may have been recognized, and that therapy should be stepped up.

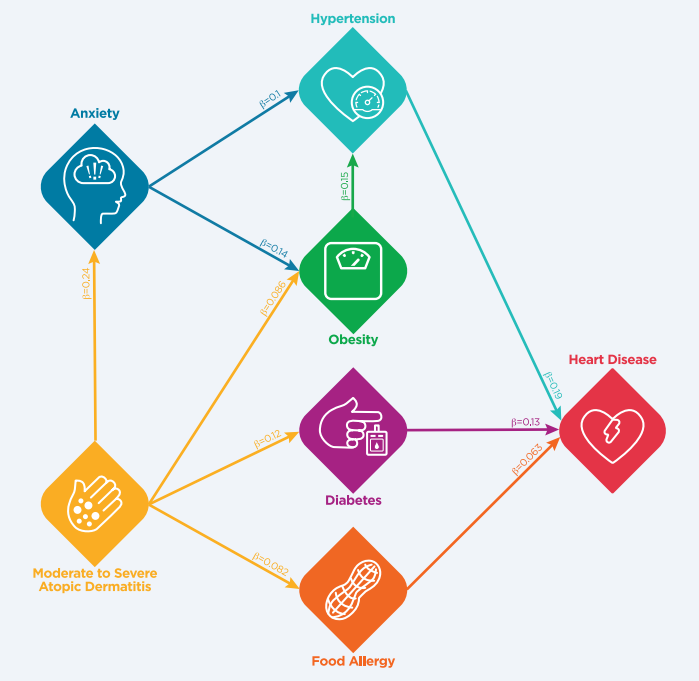
Cognitive Dysfunction

Silverberg realized it was likely that the high-impact nature of AD's signs and symptoms combined with atopic and mental health comorbidities (see below) may also impair aspects of cognitive function. As no one had yet studied this, Silverberg and his team sought to determine whether AD severity is associated with increased cognitive dysfunction, examine the predictors of cognitive dysfunction and its impact on health-related QOL (HRQOL), and evaluate the feasibility of assessing cognitive function in clinical practice using the PROMIS Cognitive Function 8-item short form. They studied 386 patients at the Multidisciplinary Eczema Clinic. At baseline, 58% reported ≥1 symptom of cognitive dysfunction in the previous 4 weeks, and dysfunction scores ranged from mild to severe. Cognitive dysfunction was associated with HRQOL scores reflecting diminished QOL, regardless of AD severity. Itch, skin pain, and sleep disturbance were the major drivers of cognitive dysfunction. With treatment, cognitive function improved as AD severity decreased. PROMIS Cognitive Function was an effective assessment tool. Further studies are needed now to determine the precise mechanisms and optimal treatment approaches for cognitive dysfunction in AD.

Comorbidities—A Complex and Multidirectional Relationship

As more is learned, the comorbidities associated with AD are turning out to present an increasingly complex picture (see illustration at right). Although obesity across the age range can develop or worsen as a consequence of AD, childhood obesity specifically appears to be a risk factor for developing AD in the first place. Type 1 diabetes in childhood actually appears to have a strong protective effect against AD, but type 2 diabetes is among the comorbidities—along with skin infections, vascular and cardiovascular phenomena, asthma and allergies, and others—that are significantly more common among AD patients of all ages. Some are direct consequences of AD. Others, eg, vascular and cardiovascular abnormalities, are secondary consequences resulting from obesity and diabetes. And AD often worsens pre-existing obesity and diabetes, which in turn further intensify the negative impact on vascular and cardiovascular variables.

Woven through this are exacerbating behavioral elements that Silverberg has discovered are more prominent among AD patients. A comprehensive literature review uncovered "strong and consistent signals for an association between AD and both active and passive smoking—although not *in utero* exposure—and with sedentary behavior," Silverberg explains. Analyzing adult patient data from the National Health Interview Survey collected in 2010 (≥27,000 patients) and 2012 (34,500 patients) showed that these signals reflect reality. Comparing adults with and without AD, those with AD definitely had increased cardiovascular risk factors and were also significantly more likely to be sedentary and to have poor health behaviors that included early-onset smoking and alcohol exposure. "So it becomes a much more complicated story," Silverberg says. "It's no longer just a health issue that we can modify therapeutically to eliminate consequences. And getting patients' skin clear is not going to magically make them want to exercise and stop smoking to reduce their cardiovascular risk. The importance of behavior modification is clear," Silverberg adds. "Even as a dermatolgist, we can encourage this."



Direct and indirect effects of AD. Structural equation models clarified the complex impact of moderate to severe AD: direct effects on food allergy, anxiety, and diabetes; direct and indirect effects on obesity, and indirect effects on high blood pressure and heart disease. (Reprinted with permission from JI Silverberg et al., *Ann Allergy Asthma Immunol.* 2018;121:604–12.)

Obesity—Before and After

Obesity had already been identified as a potential risk factor for both asthma and psoriasis, but attempts to assess this in AD were equivocal. "So we decided to look at this," Silverberg recalls. "And that ended up setting off a whole chain of research, much of which I would never have anticipated at the outset."

Silverberg looked at data from several perspectives. A retrospective case-control study using data on adult patients collected from 1994 through 2003 found obesity associated with AD. Then current data from a population-based cross section of 8,217 adults sampled from a nationally representative internet health panel clearly showed AD to be associated with higher odds of obesity. (Other comorbidities appeared as well, described below.) A systematic literature review and meta-analysis found that both overweight and obese children and adults had higher odds of developing AD. Silverberg pursued this association in pediatric AD, looking at central obesity and high blood pressure (BP) in 132 children recruited with moderate to severe disease. In this case-controlled study, AD was associated with higher body mass index, greater waist circumference, higher systolic BP, and a family history of hypertension and type 2 diabetes mellitus. Obesity actually increased the risk of AD, and among younger children it also increased the probability of more severe disease. Adult studies replicated a clear association between obesity and AD, "but its directionality is not clear," Silverberg says.

Significantly Increased Risk: Allergic Diseases, Cardiovascular Disease, and More

The large nationally representative internet health panel sample that had highlighted the prevalence of obesity among

adult AD patients also showed AD clearly associated with higher odds of asthma, hay fever, food allergy, autoimmune disease, diabetes, hypertension and other cardiovascular risk factors, and heart disease. These associations were significant even in mild and moderate AD, with still stronger effects in severe disease. Use of special models showed that moderate to severe disease has direct effects (on food allergy and diabetes), both direct and indirect effects (on obesity), and indirect effects (on hypertension, other cardiovascular risk factors, and heart disease). This portrait of risk was repeated "across multiple studies and multiple cohorts," Silverberg points out. High rates of prediabetes, hyperlipidemia, heart attack, heart failure, and stroke were also found. The weight of this evidence was startling for Silverberg, in two very different contexts.

"To see that direct path between AD and both diabetes and obesity, and then the indirect effect on blood pressure and heart disease due to that, was eye-opening," he says. "And it raises critical questions. How do these effects evolve over time? If we successfully control the AD, will this reduce the risk of diabetes and obesity, and eventually the risk for heart disease? Can more aggressive control of the skin disease and symptoms potentially prevent the risk of developing these comorbidities altogether?" He and his team have relevant studies underway.

"This is also very provocative in a much broader context," Silverberg underlines. "When this spectrum of increased risk was found in psoriasis, those involved in that research suggested that these associations reflect the inflammatory pathway involved in psoriasis—specifically an upregulation of TNF-α. But what we are seeing now," he continues, "is that this association is far more complex. It is not about any specific inflammatory pathway, but rather is an issue of chronic inflammatory disease."

And Still More

Infections: Elements associated with AD—barrier disruption, altered skin microbiome, immune dysregulation, immunosuppressive treatments, and increased bacterial colonization of the skin—increase susceptibility to infections of the skin. Silverberg wanted to see if the risk of extracutaneous infections also increases. A systematic review of published observational studies with controls, followed by a pooled meta-analysis, showed increased risk in children and adult patients for ear infections, strep throat, and urinary tract infections. Turning to the National Inpatient Sample for data on serious infections in hospitalized adult patients with and without AD, Silverberg and his team found AD linked with significantly greater odds of serious cutaneous, respiratory, multiorgan, and systemic infections. Most recently, they analyzed a 6-year span of data from close to 200,000 adults and children in the National Emergency Department Sample to see if AD is associated with risk for only a limited handful of infections or a wide array. The answer was a wide array for both age groups—higher odds of multiple bacterial, viral, fungal, and sexually transmitted (eg, genital warts, genital herpes) skin infections. The last two studies also documented the substantial additional cost once treatment becomes hospital-based. Now the goals are to identify the mechanism(s) enabling these infections, then develop prevention and treatment strategies.

Allergic contact dermatitis (ACD): In the clinic, Silverberg—who brought special expertise in contact dermatitis to his work—had found ACD to be a frequent comorbidity that added to the patient's burden. ACD is a delayed-type hypersensitivity response caused by skin contact with allergens that activate antigen-specific T cells in sensitized patients, and AD involves several predisposing elements. Skin barrier disruption facilitates the penetration of contact allergens and irritants, promoting activation of immune mechanisms that can include immune pathways common to ACD. In addition, the emollients and topical medications—including steroids—and personal care products frequently applied by AD patients often contain contact sensitizers such as propylene glycol and sorbitans, lanolin, methylisothiazolinone, neomycin, formaldehyde, sesquiterpene lactones, compositae, and fragrances.

To document the actual prevalence of ACD among AD patients, Silverberg and his team began with a systematic literature review and meta-analysis of both pediatric and adult studies. Compared to the general population, AD was associated

(Continued on page 13)

Guidelines for Effective Patient Care

1. Itch: It is critical to identify the subgroup of patients at high risk for being so overwhelmed by itching that it impairs their safety. The triggers requiring the greatest attention by clinicians are sweat, dryness, and stress. The avoidance challenge faced by patients with multiple triggers emphasizes the benefit from stepping up therapy earlier.

2. Sleep: Sleep disturbances may be underdiagnosed in the adult AD population and screening for them should be routine. A multidisciplinary approach that includes improving itch, AD severity, symptoms of allergic disease, and mental health is needed to achieve good sleep outcomes.

3. Mental health symptoms: Virtually all patients with moderate to severe AD experience significant anxiety and depression. These mental health concerns, along with suicidality, should be screened for and incorporated into clinical decision making, as getting good control of the patient's disease is key to improving these mental health issues.

4. Comorbidities: If a patient develops high-impact downstream consequences, that highlights the need to step up therapy and work to get better control of their disease.

5. QOL: Clinicians should incorporate QOL assessments in clinical practice to identify patients requiring stepped up treatment of their skin disease. SF-12 mental health and DLQI appear to have sufficient validity and feasibility for this.

NEW!

ARAZLO™
(tazarotene) Lotion, 0.045%
REDEFINE WHAT'S POSSIBLE

FOR YOUR PATIENTS WITH ACNE VULGARIS

CRACK THE TAZAROTENE CODE

ARAZLO is the first and only tazarotene lotion, formulated with polymeric emulsion technology, to help deliver the clearance you expect and the tolerability you want[1-3]

- Treatment success* rates were 26% for ARAZLO Lotion vs 13% for vehicle in study 1 and 30% vs 17%, respectively, in study 2 ($P<0.001$ in both studies)[1,4†]
- Most common adverse events (≥1% of patients and greater than vehicle) at application site were pain (5%), dryness (4%), exfoliation (2%), erythema (2%), and pruritus (1%)[1†]

SEE WHAT'S POSSIBLE AT ARAZLO.COM

*Treatment success on the Evaluator's Global Severity Score (EGSS) was defined as at least a 2-grade improvement from baseline and an EGSS score of clear (0) or almost clear (1).[1]

†**Phase 3 study design:** The safety and efficacy of ARAZLO Lotion were assessed in 2 multicenter, randomized, double-blind clinical trials of 1,614 subjects aged 9 years and older with facial acne vulgaris. Subjects had a score of moderate (3) or severe (4) on the EGSS, 20 to 50 inflammatory lesions, 25 to 100 noninflammatory lesions, and 2 or fewer facial nodules.[1]

Indication

ARAZLO™ (tazarotene) Lotion, 0.045% is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

Important Safety Information

ARAZLO Lotion is for topical use only. Not for oral, ophthalmic, or intravaginal use.

Contraindication

ARAZLO Lotion is contraindicated in pregnancy due to the potential harm to the fetus.

Warnings and Precautions

Embryofetal Risk Females of childbearing potential should be warned of the potential risk and should use adequate birth-control measures when ARAZLO Lotion is used. A negative result for pregnancy should be obtained within 2 weeks prior to ARAZLO Lotion therapy, and therapy begun during a menstrual period. If the patient becomes pregnant while using ARAZLO Lotion, treatment should be discontinued.

Skin Irritation Patients using ARAZLO Lotion may experience application site pain, dryness, exfoliation, erythema, and pruritus. Depending upon severity, adjust or interrupt dosing as needed, increasing or resuming treatment as tolerated. Avoid application of ARAZLO Lotion to eczematous or sunburned skin.

Photosensitivity and Risk for Sunburn Minimize unprotected exposure to ultraviolet light, including sunlight, sunlamps and tanning beds, during the use of ARAZLO Lotion. Warn patients with high levels of sun exposure and those with inherent sensitivity to sun to exercise caution. Instruct patients to use sunscreen products and protective clothing over treated areas when sun exposure cannot be avoided.

ARAZLO Lotion should be administered with caution if the patient is taking drugs known to be photosensitizers (eg, thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Weather extremes, such as wind or cold, may be more irritating to patients using ARAZLO Lotion.

Adverse Reactions The most common adverse reactions (in ≥1% of patients and greater than vehicle) were: application site pain, dryness, exfoliation, erythema, and pruritus.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch Health US, LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Brief Summary of full Prescribing Information on following page.

References: 1. ARAZLO Lotion [prescribing information]. Bridgewater, NJ. Bausch Health US, LLC. **2.** Tanghetti EA, Kircik LH, Green LJ, et al. A phase 2, multicenter, double-blind, randomized, vehicle-controlled clinical study to compare the safety and efficacy of a novel tazarotene 0.045% lotion and tazarotene 0.1% cream in the treatment of moderate-to-severe acne vulgaris. *J Drugs Dermatol*. 2019;18(6):542-548. **3.** Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed October 10, 2019. **4.** Data on file.

Ortho Dermatologics

ARAZLO™ (tazarotene) lotion, for topical use
Initial U.S. Approval: 1997
This Brief Summary does not include all the information needed to use ARAZLO safely and effectively; please see full Prescribing Information for ARAZLO.

INDICATIONS AND USAGE

ARAZLO™ (tazarotene) lotion, 0.045% is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

CONTRAINDICATIONS

ARAZLO is contraindicated in pregnancy. ARAZLO may cause fetal harm when administered to a pregnant patient *[see Warnings and Precautions, Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Embryofetal Toxicity Based on data from animal reproduction studies, retinoid pharmacology and the potential for systemic absorption, ARAZLO may cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. Safety in pregnant patients has not been established. The potential risk to the fetus outweighs the potential benefit to the mother; therefore, discontinue ARAZLO as soon as pregnancy is recognized.

Tazarotene elicits malformations and developmental effects associated with retinoids after topical and oral administration to pregnant rats and rabbits during organogenesis. However, limited case reports of pregnancy in females enrolled in clinical trials for ARAZLO have not reported a clear association with tazarotene and major birth defects or miscarriage risk *[see Contraindications, Use in Specific Populations]*.

Systemic exposure to tazarotenic acid is dependent upon the extent of the body surface area treated. In patients treated topically over sufficient body surface area, exposure could be in the same order of magnitude as in orally treated animals. Tazarotene is a teratogenic substance in animals, and it is not known what level of exposure is required for teratogenicity in humans.

Advise pregnant patients of the potential risk to a fetus. Obtain a pregnancy test within 2 weeks prior to ARAZLO therapy. Initiate ARAZLO therapy during a menstrual period. Advise patients of childbearing potential to use effective contraception during treatment with ARAZLO *[see Dosage and Administration, Use in Specific Populations]*.

Skin Irritation Patients using ARAZLO may experience application site pain, dryness, exfoliation, erythema, and pruritus. Depending upon severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of the application of ARAZLO, or discontinue use. Therapy can be resumed, or the frequency of application can be increased, as the patient becomes able to tolerate treatment.

Avoid use of concomitant medications and cosmetics that have a strong drying effect. It is recommended to postpone treatment with ARAZLO until the drying effects of these products subside.

Avoid application of ARAZLO to eczematous or sunburned skin.

Photosensitivity and Risk for Sunburn Because of heightened burning susceptibility, minimize unprotected exposure to ultraviolet light including sunlight and sunlamps during the use of ARAZLO. Warn patients who normally experience high levels of sun exposure and those with inherent sensitivity to sun to exercise caution. Use sunscreen products and protective clothing over treated areas when sun exposure cannot be avoided. Patients with sunburn should be advised not to use ARAZLO until fully recovered.

ARAZLO should be administered with caution if the patient is taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Weather extremes, such as wind or cold, may be more irritating to patients using ARAZLO.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in more detail in other sections:

- Embryofetal toxicity *[see Warnings and Precautions]*
- Photosensitivity and Risk of Sunburn *[see Warnings and Precautions]*

Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In 2 multicenter, randomized, double-blind, vehicle-controlled clinical trials, subjects age 9 years and older applied ARAZLO or vehicle once daily for 12 weeks. The majority of subjects were White (74%) and female (66%). Approximately 22% were Hispanic/Latino and 42% were younger than 18 years of age, fourteen of 779 subjects (1.8%) treated with ARAZLO were between 9 years to less than 12 years of age. Adverse reactions reported by ≥1% of subjects treated with ARAZLO and more frequently than subjects treated with vehicle are summarized in Table 1. Most adverse reactions were mild to moderate in severity. Severe adverse reactions represented 1.3% of the subjects treated. Overall, 2.4% (19/779) of subjects discontinued ARAZLO because of local skin reactions.

Table 1: Adverse Reactions Reported by ≥1% of the ARAZLO Group and More Frequently than the Vehicle Group

Adverse Reactions N (%)		
	ARAZLO Lotion N=779	**Vehicle N=791**
Application site pain[1]	41 (5)	2 (<1)
Application site dryness	30 (4)	1 (<1)
Application site exfoliation	16 (2)	0 (0)
Application site erythema	15 (2)	0 (0)
Application site pruritus	10 (1)	0 (0)

[1]Application site pain defined as application site stinging, burning, or pain

Skin irritation was evaluated by active assessment of erythema, scaling, itching, burning and stinging, with grades for none, mild, moderate, or severe. The maximum severity generally peaked at Week 2 of therapy and decreased thereafter. The percentage of subjects with these signs and symptoms at any post-baseline visit are summarized in Table 2.

Table 2: Incidence of Local Cutaneous Irritation at any Post-Baseline Visit

	ARAZLO Lotion N=774 Mild/Moderate/Severe	**Vehicle Lotion N=789** Mild/Moderate/Severe
Erythema	49%	38%
Scaling	51%	23%
Itching	29%	14%
Burning	30%	6%
Stinging	22%	5%

DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted with ARAZLO.

Concomitant use with oxidizing agents, as benzoyl peroxide, may cause degradation of tazarotene and may reduce the clinical efficacy of tazarotene.

In a trial of 27 healthy female subjects, between the ages of 20–55 years, receiving a combination oral contraceptive tablet containing 1 mg norethindrone and 35 mcg ethinyl estradiol, the concomitant use of tazarotene administered as 1.1 mg orally (mean ± SD C_{max} and AUC_{0-24} of tazarotenic acid were 28.9 ± 9.4 ng/mL and 120.6 ± 28.5 ng•hr/mL, respectively) did not affect the pharmacokinetics of norethindrone and ethinyl estradiol over a complete cycle.

The impact of tazarotene on the pharmacokinetics of progestin only oral contraceptives (i.e., minipills) has not been evaluated.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary ARAZLO is contraindicated in pregnancy.

There are no available data on ARAZLO use in pregnant patients to inform a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, ARAZLO may cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. The potential risk to the fetus outweighs the potential benefit to the mother; therefore, ARAZLO should be discontinued as soon as pregnancy is recognized.

In animal reproduction studies with pregnant rats, reduced fetal body weights and reduced skeletal ossification were observed after topical administration of a tazarotene gel formulation during the period of organogenesis at a dose equivalent to the maximum recommended human dose (MRHD) (based on AUC comparison). In animal reproduction studies with pregnant rabbits, single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were observed after topical administration of a tazarotene gel formulation at 15 times the MRHD (based on AUC comparison) *(see Data)*.

In animal reproduction studies with pregnant rats and rabbits, malformations, fetal toxicity, developmental delays, and/or behavioral delays were observed after oral administration of tazarotene during the period of organogenesis at doses 1 and 30 times, respectively, the MRHD (based on AUC comparison). In pregnant rats, decreased litter size, decreased numbers of live fetuses, decreased fetal body weights, and increased malformations were observed after oral administration of tazarotene prior to mating through early gestation at doses 6 times the MRHD (based on AUC comparison) *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of major birth defects, loss, and other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data In an embryofetal development study in rats, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rats during gestation days 6 through 17. Reduced fetal body weights and reduced skeletal ossification occurred at this dose (equivalent to the MRHD based on AUC comparison). In an embryofetal development study in rabbits, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rabbits during gestation days 6 through 18. Single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were noted at this dose (15 times the MRHD based on AUC comparison).

When tazarotene was given orally to animals, developmental delays were seen in rats; malformations and post-implantation loss were observed in rats and rabbits at doses producing 1 and 30 times, respectively, the MRHD (based on AUC comparison).

In female rats orally administered 2 mg/kg/day of tazarotene from 15 days before mating through gestation day 7, classic developmental effects of retinoids including decreased number of implantation sites, decreased litter size, decreased numbers of live fetuses, and decreased fetal body weights were observed at this dose (6 times the MRHD based on AUC comparison). A low incidence of retinoid-related malformations was observed at this dose.

In a pre- and postnatal development toxicity study, topical administration of a tazarotene gel formulation (0.125 mg/kg/day) to pregnant female rats from gestation day 16 through lactation day 20 reduced pup survival, but did not affect the reproductive capacity of the offspring. Based on data from another study, the systemic drug exposure in the rat at this dose would be equivalent to the MRHD (based on AUC comparison).

Lactation

Risk Summary There are no data on the presence of tazarotene or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. After single topical doses of a ^{14}C-tazarotene gel formulation to the skin of lactating rats, radioactivity was detected in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ARAZLO and any potential adverse effects on the breastfed child from ARAZLO.

Clinical Considerations To minimize potential exposure to the breastfed infant via breast milk, use ARAZLO for the shortest duration possible while breastfeeding. Advise breastfeeding patients not to apply ARAZLO directly to the nipple and areola to prevent direct infant exposure.

Females and Males of Reproductive Potential

Pregnancy Testing Pregnancy testing is recommended for patients of childbearing potential within 2 weeks prior to initiating ARAZLO therapy which should begin during a menstrual period.

Contraception Advise patients of childbearing potential to use effective contraception during treatment with ARAZLO.

Pediatric Use Safety and effectiveness of ARAZLO for the topical treatment of acne vulgaris have been established in pediatric patients age 9 years and older based on evidence from two multicenter, randomized, double-blind, parallel-group, vehicle-controlled, 12-week clinical trials and an open-label pharmacokinetic study. A total of 300 pediatric subjects aged 9 to less than 17 years received ARAZLO in the clinical studies *[see Clinical Pharmacology and Clinical Studies]*.

The safety and effectiveness of ARAZLO in pediatric patients below the age of 9 years have not been established.

Geriatric Use Clinical trials of ARAZLO did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

OVERDOSAGE

Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids. If oral ingestion occurs, monitor the patient closely and administer appropriate supportive measures, as necessary.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter-term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to the MRHD (based on AUC comparison).

A long-term study with topical application of up to 0.1% of tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals. Tazarotenic acid systemic exposures at the highest dose was 7 times the MRHD (based on AUC comparison).

Tazarotene was non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in human lymphocytes. Tazarotene was non-mutagenic in CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in an in vivo mouse micronucleus test.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of a tazarotene gel formulation up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat at the highest dose was equivalent to the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of tazarotene up to 1 mg/kg/day which produced a systemic exposure 4 times the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through gestation day 7 with oral doses of tazarotene up to 2 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose which produced a systemic exposure 6 times the MRHD (based on AUC comparison).

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with higher rates of positive epicutaneous patch tests and ACD appeared to be more common in these patients. Next, Silverberg carried out a retrospective chart review of roughly 500 adult patients—21.5% of whom had AD, 21.7% who had had it in the past—who had been patch tested to an expanded allergen series during 2014–2017. What set AD patients apart was significantly more positive reactions to ingredients in their personal care products and topical medications, and more frequent sensitivity to multiple ingredients in these topical products. Lesion distribution was also different (see illustration below). Silverberg is currently assessing the impact of contact allergen avoidance on the clinical course and severity of AD.

Because ACD can mimic the clinical presentation of AD, patch testing should be considered in adolescent or adult-onset AD with worsening or more generalized dermatitis, localized or atypical lesional distribution, refractory disease, or when AD worsens with topical therapy. It should also be done prior to systemic immunosuppressive treatment. Silverberg recommends an expanded patch-testing series that includes the allergens common for AD patients.

ADD/ADHD: Previous analyses in children had found a consistent association between AD and ADD/ADHD, but contributing factors had not been explored, nor had this been assessed in adults. Silverberg and his research team analyzed data merged from 19 U.S. population-based surveys for 354,416 children (2–17 years) and 34,613 adults (age 18+). Results confirmed a greater incidence of ADHD in pediatric patients. Severe AD and sleep disturbance independently and synergistically contribute to this risk. Obesity, headaches, and anemia increase it further. Adult AD patients are also at greater risk for ADHD, which is heightened by asthma, headaches, and insomnia. The mechanism underlying this increased risk is unknown.

Osteopenia/osteoporosis: An earlier population study of adult patients with a self-reported diagnosis of AD had identified an increased risk. Silverberg confirmed this with a physician-diagnosed patient sample. The major risk factors—including corticosteroid use, reduced physical activity, and chronic inflammation—have to be clarified, and optimal risk-reduction strategies identified.

Screen For Comorbidities

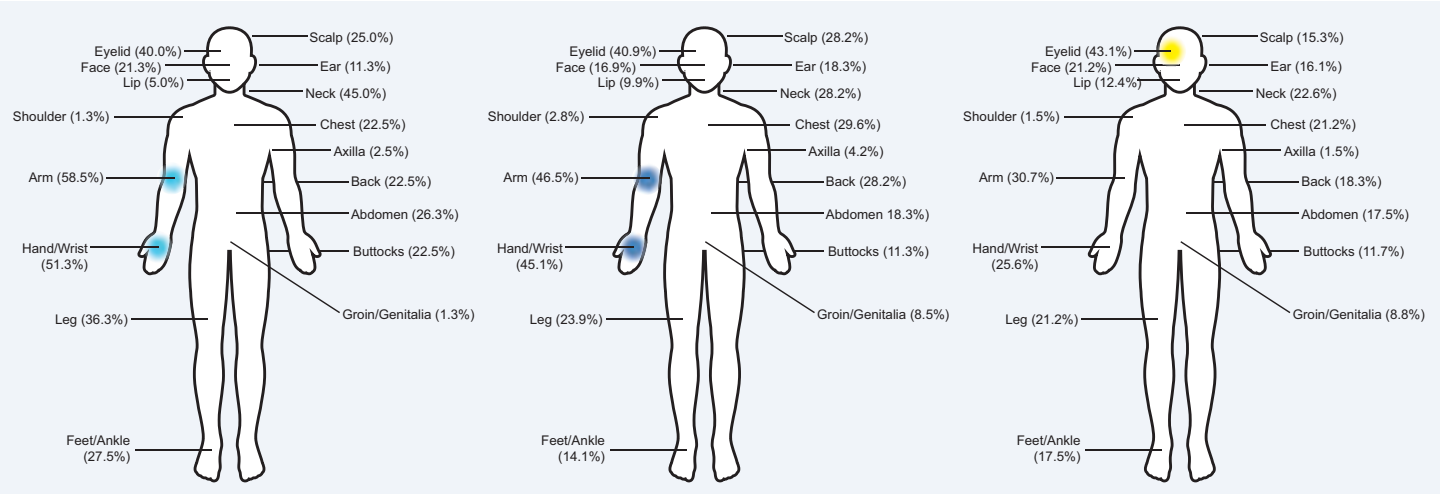
To translate this documentation of significant comorbid health problems into effective clinical practice, Silverberg emphasizes that screening to identify them—the range of other atopic disorders, infections, cardiovascular risks, obesity, and diabetes—at the outset is essential for proper disease management, and for improving patient longevity and overall health. Refer patients to the appropriate providers for management. "It is also critical to understand these comorbidities from the perspective of the burden of disease," Silverberg underlines. "When patients develop high-impact downstream consequences, that highlights the need to step up therapy and work to get better control of their disease."

Disease Burden and Quality of Life

Silverberg had determined that the disease burden in AD reflects the dynamics of a complex of factors synergistically merging the impact of intense and wide-ranging symptoms (including itch, skin pain, sleep disturbance, cognitive dysfunction, and mental health issues), diminished health from comorbidities, and psychological stress from the appearance of lesional skin. Physical and social functioning are impaired, work capabilities are diminished, and the potential for accidents is increased, and this intense stress can further worsen symptoms. Thus it is essential to assess each patient's burden and QOL.

Because the patient burden of AD is so multifactorial, it cannot be assessed by signs and symptoms alone. Numerous instruments had been developed to assess burden and its impact, but AD-specific tools had not yet been validated, and those that were skin-specific or generic health-related QOL instruments had not been validated for AD. Silverberg addressed this, and found that the SF-12 mental component and the DLQI are useful in a clinical setting for assessing burden and QOL in AD.

Then, his goal was to arrive at a more definitive sense of this impact and how it compares with that of other chronic health disorders. Silverberg and his team approached their assessment of a population-based cross section of 602 adult patients with several hypotheses: (1) that AD is associated with impaired QOL; (2) that this impairment is greater than for other common chronic diseases; (3) that patients combining severe skin lesions, high frequency of symptoms, and severe pruritus



ACD lesions and AD. The distribution of skin lesions is similar between patients with current AD *(left)* and past AD *(middle)*, with arms and hands/wrists the most commonly affected areas. For those with no history of AD, eyelid lesions are the most common. (Reprinted from S. Rastogi et al., *J Amer Acad Dermatol.* 2018;79:1028–33, with permission from Elsevier.)

have a greater QOL decrement compared with those having only one/none of these components; and (4) that moderate/severe AD is associated with poor QOL independent of mental health symptoms and atopic pathologies. Silverberg used five patient-reported measures—including assessments of both itch and sleep—to determine disease and symptom severity. And he used the SF-12 mental and physical health scores and the DLQI to assess health-related QOL.

"We found that adults with AD had a lower overall health rating and life satisfaction, significantly lower SF-12 mental health subscores, and higher DLQI scores—and all of these indicate significant QOL impairment," Silverberg points out. In a large patient subset, AD limited patients' lifestyle, led to avoidance of social interaction, and impacted their activities—and virtually all of these outcomes were associated with AD severity. The most burdensome symptoms that patients reported were itch (54.4%), excessive dryness/scaling (19.6%), and red/inflamed skin (7.2%). This same picture remained after carefully controlling for all variables with the potential for influencing the results. "Together, these results indicate that AD—especially moderate-to-severe disease—is associated with a profound patient burden among U.S. adults," Silverberg notes. Moderate and severe AD were associated with dramatically lower QOL than all of the other chronic disorders examined in this study. "We strongly recommend that clinicians incorporate QOL assessments in clinical practice to identify patients requiring step-up treatment of their skin disease," Silverberg states.

Measuring the Realities: The Patient Knows Best

Managing an individual patient's disease successfully requires an accurate awareness of symptoms and comorbidities and their severity, and their contributions to the overall impact on the patient's QOL. Because AD is such a heterogeneous and complex disease, no single assessment instrument can accomplish an objective clinical evaluation and solicit the patient's experiences and perceptions of the multiple aspects of living with their disease. A huge slew of tests exists, but mostly for trial use and largely unvalidated. The work to create an ideal and standardized menu of tests is in progress, and Silverberg is central to this effort. He systematically evaluates and compares existing tests, develops severity strata to facilitate interpretable results, and develops new tests to fill significant gaps. One example is the PROMIS item bank PIQ-Itch, which specifically addresses itch in the context of AD. His guiding precepts involve patient-responsive questionnaires that are simple to use and to score, and provide results relevant to both clinical and trial settings.

Silverberg is also an active member of **HOME**—the highly diverse international consensus group ***H****armonising* ***O****utcome* ***M****easures for* ***E****czema*—that is dedicated to developing a consensus-based *core outcome set (COS)* for clinical practice and trials, and defining the minimum that should be measured in all clinical trials. HOME includes healthcare professionals, journal editors, regulatory authorities, pharmaceutical industry representatives, and patients.

AD's Complexity: The Skin and Beyond

It is now clear that although AD is a disease that manifests on the skin, its broader impact and implications go well beyond. Pivotal for the clinician now is that evaluating a patient involves far more than noting obvious symptoms and scoring lesional skin. "For starters, this includes screening for potential experiential and behavioral correlates and possible associated medical issues, and utilizing patient-reported assessments," Silverberg points out. "This will substantially improve the clinician's ability to evaluate and understand each patient meaningfully and manage their AD effectively." Ultimately, he hopes to find a way of translating this newly recognized complexity into a clinically relevant tool that can be used to tailor and optimize therapy, and to periodically monitor treatment impact. "This will have a profound impact on patient care," Silverberg says.

Silverberg intends to take this ability still further. "Although I maintain a burning interest in all of the areas that I have been investigating, and will continue to explore them, I really look forward to exploring this issue of complexity more actively," he says. One focus involves the noncutaneous downstream consequences of AD, such as sleep disturbance and mental health symptoms and cardiovascular comorbidities. "It is essential to understand these downstream effects," he explains, "because we may be able to identify patient subsets that are particularly at risk for specific issues, and actually intervene early on to mitigate them."

Evolving Perspective: A Much Bigger Picture

"I have become aware of so many nuances in AD," Silverberg reflects. "And I look at the distributions of different phenotypes around the world, and the mechanistic data coming out now that point to different underlying mechanisms. I find myself thinking that AD is really a spectrum of diseases that we lump together under a single umbrella because of certain common clinical features, and that we are ultimately going to be talking about a far more heterogeneous and complicated disease than we have traditionally conceived. It's very likely that this incredibly complex disease holds even greater variety than we have found for psoriasis. Clinically," he notes, "we are drawn to the idea of a one-size-fits-all algorithm for diagnosis and treatment. But the more that I study AD, the more I realize that there is far too much complexity for this ever to happen. We have new targeted medications in development," he continues, "but I do not know how we will get the right medication to the right patient if we lack a real understanding of the different phenotypes. We need to develop a better grasp of the nuances, the granularity of this disease. And the evolution of precision medicine will provide the appropriate context for this progress," Silverberg concludes.

Looking Beyond AD

Silverberg has several broader goals as well. He is targeting chronic itch—which is so life-altering for patients—by working to develop improved assessments that will help dermatologists understand how best to reduce a given patient's itch. He intends to improve our understanding of the direct and indirect burden of the spectrum of inflammatory skin diseases, including their relationship with other health conditions, such as cardiovascular disease. And finally, "I am hoping to identify novel modifiable risk factors for inflammatory skin diseases, and then develop clinical and epidemiological interventions to prevent them," Silverberg says.

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Final Comment

Silverberg sums up the vast range of his research and his continuing progress in filling in the many knowledge gaps in AD. "I don't know that I can take credit for any of these ideas," he insists. "They all come from listening to my patients. That is what drives me!"

Suggested Readings

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The Board of Trustees is very pleased to present the slate of officers formally elected this spring. The 2020 officers reflect both continuity and transition. They all share a long history of commitment to helping the Dermatology Foundation fortify its ability to support the research that advances patient care.

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