DESIGNATING APRIL as Rosacea Awareness Month, the National Rosacea Society aims to increase public understanding of the condition and lead individuals who may be affected to seek medical help before their condition becomes worse. Delivering optimal management for each patient will require undertaking a comprehensive assessment to identify all of the individual’s rosacea-related signs.

As the world continues to fight the spread of the novel coronavirus and its resulting illness COVID-19, governments and the scientific community are racing to identify new and existing drugs that might help to flatten the curve and save lives. As of Wednesday, March 25, 2020, the CDC reports there have been a total of 54,453 individuals in the United States infected with COVID-19 and 737 deaths. Worldwide, the virus has infected 416,916 individuals, resulting in nearly 19,000 deaths, according to the European Centre for Disease Control and Prevention, posing a serious global health threat.

While there are no drugs approved to treat, cure or prevent COVID-19, at this time, there are several potential treatments that may help ease the symptoms from a supportive care perspective, according to the U.S. Food and Drug Administration in a March 19 press release. The organization says it is working...
COVID-19 WAR

READ MORE ON THE COVID-19 WAR

HCQ data may support use in treatment
Experts advise caution on early, emerging data
Impact of lifting restrictions
AAD resource center supports members
Biologic therapy guidance during pandemic
Adolescent disease burden
Impact mirrors severity in EPI-CARE study

Rosacea
Combination Tx, patient ed keys to optimize care

Atopic dermatitis
Combination Tx, patient ed keys to optimize care

Skin cancer
Targeted therapy for advanced BCC
Oral hedgehog inhibitors effective treatment options.

Psoriasis
Abrocitinib offers quick symptom relief
Investigational therapy improved severity at 12 weeks.

Lifestyle recommendations
Factors that may curb symptoms.

Acne
More treatment options
New topical, oral products available across medication categories.

Antibiotic therapy
Prescribing should consider potential for bacterial resistance.

Rosacea
Pivotal trials positive
Phase 2 results show novel topical foam safe, effective.

Combination strategies
Dual regimens may provide faster improvement and better efficacy.

Aging
Hair loss treatment controversies, concerns
Expert highlights data to aid treatment decisions.

Microneedling plus radiofrequency
Combination treats acne scars, traumatic scars, wrinkles and laxity and can be used regardless of skin phototype.
Annenberg Circle Sustaining Members
A $5,000 Annual Contribution Beyond Completed Pledge of $25,000

$125,000
Murad Alam, M.D.
Robert B. Ash, M.D.*
Andrew K. Bean, M.D.*

David R. Bickers, M.D.*
Jennifer C. Cather, M.D.*
Karynne O. Duncan, M.D.*

Peter G. Ehrnstrom, M.D.*
James O. Ertle, M.D.*
Howard Murad, M.D.*

Thomas G. Olsen, M.D.*
Bruce U. Wintroub, M.D.*

$75,000
Rodney S.W. Basler, M.D.*
Eugene A. Bauer, M.D.*
Ronald R. Brancaccio, M.D.
Jeffrey P. Callen, M.D.*
Valerie D. Callender, M.D.
S. Wright Caughman, M.D.
Kevin D. Cooper, M.D.*
Lynn A. Cornelius, M.D.
Gregory J. Cox, M.D.*
Peggy S. Crawford, M.D.
W. Christopher Duncan, M.D.
Michael J. Ebertz, M.D.*
Richard L. Edelson, M.D.
Janet A. Fairley, M.D.
Patrick R. Feehan, M.D.*

Alvin E. Friedman-Kien, M.D.
Maria C. Garzon, M.D.*
C. William Hanke, M.D.
James J. Herrmann, M.D.*
Julie A. Hodge, M.D., Ph.D.*
Mark J. Holzberg, M.D.
Waine C. Johnson, M.D.
Sewon Kang, M.D., Ph.D.*
Robert S. Kirsner, M.D., Ph.D.*
Jennifer C. Cather, M.D.
Karynne O. Duncan, M.D.*

Donald J. Miech, M.D.
D. Scott Miller, M.D.*
Douglas N. Naversen, M.D.*
Seth J. Orlow, M.D., Ph.D.*
Nicholas V. Perricone, M.D.*
Phoebe Rich, M.D.
Rudolf R. Roth, M.D.*
James T. Sandwich, M.D.*
William S. Sawchuk, M.D.
Christopher R. Shea, M.D.
David N. Silvers, M.D.
Stephen C. Somach, M.D.
Thomas A. Stasko, M.D.
William A. Steele, M.D.*
Robert A. Swerlick, M.D.

Helen M. Torok, M.D.*
James L. Troy, M.D.
Donald S. Waldorf, M.D.*
Susan H. Weinkle, M.D.*
Jonathan S. Weiss, M.D.
George B. Winton, M.D.
Kim B. Vancey, M.D.
Ruth A. Yates, M.D.
Melanie L. Zahner, M.D.*
James A. Zalla, M.D.*
John J. Zone, M.D.

FROM THE PUBLIC
Mitchell S. Wortzman, Ph.D.*

$50,000
Timothy G. Berger, M.D.
Roger I. Ceilley, M.D.*
Richard A. Clark, M.D.
David J. Clemons, M.D.
Mark G. Cleveland, M.D., Ph.D.
Gerald E. Cooley, M.D.
George Cotsarelis, M.D.*
Jeffrey S. Dover, M.D.*
Ronald E. Grimwood, M.D.

Mark D. Herron, M.D.
Howard C. Hines, M.D.*
Carol L. Huang, M.D.
Tim Ioannides, M.D.
Gail A. Klemman, M.D.
E. Michael Kramer, M.D.
Joseph C. Kvedar, M.D.*
Ali Moini, M.D.
Angela Yen Moore, M.D.

George J. Murakawa, M.D., Ph.D.
Paul T. Nghiem, M.D., Ph.D.*
Maritza I. Perez, M.D.
Oliver M. Reed, M.D.*
M. Joyce Rico, M.D.*
Jennifer M. Ridge, M.D.
Mark P. Seraly, M.D.*
Kanade Shinkai, M.D., Ph.D.*
Michael T. Siegel, M.D.

Vera Y. Soong, M.D.
Marica G. Tonnensen, M.D.
Julian J. Trevino, M.D.
Allison T. Vidimos, M.D.
Heidi A. Waldorf, M.D.*
Kent D. Walker, M.D.
Kathleen M. Welsh, M.D.
Barbara Dahl Wilson, M.D.*
Scott L. Zahner, M.D.*

$30,000
Tina S. Alster, M.D.*
Mathijs H. Brentjens, M.D.
Maxwell A. Fung, M.D.
Sharon A. Glick, M.D.
Bhushan D. Hardas, M.D., Ph.D.

William D. James, M.D.
Kay S. Kane, M.D.
Norman A. Lockshin, M.D.
Elizabeth P. Berry Long, M.D.
M. Alan Menter, M.D.*

Caren F. Mikesh, M.D.
Robert J. Pariser, M.D.
Frank Parker, M.D.
Stephen M. Purcell, D.O.
Beata L. Rydzik, M.D.

Ava T. Shamban, M.D.
Alan K. Silverman, M.D.
Gregory W. Thompson, M.D.
Angela B. Wingfield, M.D.
A Commitment of $25,000

James E. Elder, M.D.
Bori E. Elewski, M.D.*
Craig A. Elneys, M.D.
Christophor B. Harmon, M.D.
Patricia Sanders Jackson, M.D.
J. Alan Long, M.D.
Amy Markert Morris, M.D.
Lon F. Raby, Jr., M.D.
Laura McKeely Tamburn, M.D.
Julian Morris, M.D.
Thomas M. Thomas, M.D.
George G. Tisdale, M.D.
J. Scott VanLoock, M.D.

Margaretta A. O'Reilly, M.D.

Evans G. Bauer, M.D.
Paul W. Becker, M.D.
Suzanne M. Connolly, M.D.
Paul E. English, M.D.
Marc I. Epstein, D.O.
David N. Rieger, M.D.
John H. Haraldsen, M.D.
Michael J. Huether, M.D.
Ira Lawrence, M.D.
Roy S. Rogers, III, M.D.

Phyllis K. Murphy, M.D.
Susana M. Leal-Khouri, M.D.
Alexander P. Kowalczyk, M.D.
Timothy M. Kilpatrick, M.D.
John R. Hamill, Jr., M.D.
Phillip Frost, M.D.
Robert J. Friedman, M.D.
Judith E. Crowell, M.D.
Christopher P. Crotty, M.D.
James B. Connors, M.D.
Leslie S. Baumann, M.D.
Elizabeth L. Tanzi, M.D.
Maurice A. Thew, M.D.

LeRoy G. Carney, Jr., M.D.
Tracy M. Campbell, M.D.
Clarence W. Brown, Jr., M.D.
Joel E. Bernstein, M.D.
Thomas W. Andrews, M.D.
William K. Wong, M.D.
Stella S. Matsuda, M.D.
Janice M. Warner, M.D.
Betsy N. Perry Thacker, M.D.
Richard L. Sturm, M.D.
Joel Stephen Shavin, M.D.
Michael J. Sharkey, M.D.
Joel S. Sturm, M.D.
Hiram M. Sturm, M.D.
Stephen L. Sturm, M.D.
Stephanie F. Templeton, M.D.
Betsy N. Perry Thacker, M.D.
Janice M. Warner, M.D.
Jamie D. Weisman, M.D.
James A. Yeckley, M.D.

Leslie S. Baumans, M.D.
Betsy B. Beres, M.D.
James B. Connors, M.D.
Christopher P. Crotty, M.D.
Judith E. Crowell, M.D.
Ana M. Duarte, M.D.
Craig J. Eichler, M.D.
Anna F. Falabella, M.D.
Michael J. Freeman, M.D.
Robert J. Friedman, M.D.
Philippe Frost, M.D.*

Brad P. Glick, D.O., M.H.P.
John R. Hamill, Jr., M.D.
Timothy M. Kilpatrick, M.D.
Alexander P. Kowalczyk, M.D.
Susan M. Leaf-Khouri, M.D.
Dieter Manstein, M.D.
Laetitia A. Manuelli, M.D.
Russell D. Metz, M.D.
Richard A. Miller, M.D.
Richard Kotapati, M.D.
Phyllis K. Murphy, M.D.

Christopher G. Nelson, M.D.
Douglas N. Robbins, M.D.
Leslie S. Baumans, M.D.
Joseph F. Seber, M.D.
Anil H. Singh, M.D.
Laura E. Skelliecock, M.D.*
Kristin W. Smallwood, M.D.
K. L. Spear, M.D.
Roger H. Stewart, M.D.
John M. Strasser, M.D., M.P.H.
Cynthia R. Strohmeier, M.D.
Michael D. Tharp, M.D.
Abel Torres, M.D.
Panos E. Vassiloudes, M.D., Ph.D.
Jennifer L. Vesper, M.D.
Nardo Zaias, M.D.

Julian Morris, M.D.
Thomas M. Thomas, M.D.
George G. Tisdale, M.D.
J. Scott VanLoock, M.D.
Margaretta A. O'Reilly, M.D.

Peter A. Pollat, M.D.*
C. Ralph Daniel, III, M.D.
Sabra S. Sullivan, M.D., Ph.D.

Susan K. Ailer, M.D.
Jacquelyn B. Garrett, M.D.
Victoria Gunn, M.D.
John C. Hall, M.D.
Mark A. Hurt, M.D.
Peter J. Muelleman, M.D.
William V. Stoecker, M.D.
Howard G. Welgis, M.D.

Robert T. Bradell, M.D.*
C. Ralph Daniel, III, M.D.

Sharon A. Galvin, M.D.
William F. Cosulich, M.D.

Suzanne W. Braddock, M.D.
David N. Kingsley, M.D.
Joel Schlessinger, M.D.
David J. Watts, M.D.

James Q. Del Rosso, D.O.
Curt P. Samlaska, M.D.

Suzanne W. Braddock, M.D.
David N. Kingsley, M.D.
Joel Schlessinger, M.D.
David J. Watts, M.D.

James Q. Del Rosso, D.O.
Curt P. Samlaska, M.D.
STAY VIGILANT
TO PROTECT
PRACTICE, PATIENTS

by MIKE HENNESSY, SR.

AT THE TIME of this publication, the national COVID-19 pandemic continues to mount. Across the country, schools and businesses have closed, and workers have moved their headquarters to home offices as businesses have closed doors, and several states have issued “stay-at-home” orders.

As the national pandemic continues to escalate, with new cases and findings about the virus that results in COVID-19 infection coming daily, new insights are revealing the implications on dermatology practices and patients. In combating the pandemic, dermatologists must take critical steps to adapt operations while still providing essential patient care and preventing exposure in office settings, experts say.

In this issue, we’ve put together a snapshot-in-time update about the status of the outbreak to date, and what dermatologists can do to safeguard practices while still providing essential care. We’re sharing important information about an anti-malaria drug that may provide a benefit in this war on the new coronavirus; however, more evidence is still required before it can be officially recommended as a treatment. We’ve outlined a message to members, released March 19, by George Huza, M.D., immediate past president of the American Academy of Dermatology (AAD), who shared the latest insight related to the dermatology specialty, which includes guidance on self-protection, as well as the protection of staff and patients.

Among the resources provided, are tips for patient screenings and effective disinfecting solutions for use around the clinic based on guidance from the Centers for Disease Control (CDC) and the World Health Organization (WHO). To maintain spaces and prevent viral transfer, staff should regularly wipe down all chairs and arm rests, exam room tables, counters, doorknobs, light buttons and handles, faucet handles, all bath-room surfaces, reception area counters, all lab sur-faces, and all kitchen area surfaces; keep trash cans empty and wipe down the inside and outside of containers regularly and thoroughly.

If a physician suspects a patient’s symptoms could indicate a COVID-19 infection, the patient should be immediately isolated and proper steps should be taken to confirm infection and to notify the local or state health department.

AAD has compiled detailed resources related to the pandemic for members, which can be found at www.aad.org/coronavirus. The organization is develop-ing further guidance for members related to personnel issues and will provide updates as that infor-mation becomes available.

As this is top of mind, we will continue to follow the developments and update you through our web-site and enewsletters. More information on manag-ing infection risk, clinic operations and staffing can also be found from the following national resources:

• AAD: Coronavirus Resources/Managing your prac-tice through the COVID-19 outbreak
• CDC: Interim Infection Prevention and Control Rec-ommendations
• CDC: Steps Healthcare Facilities Can Take
• WHO: The COVID-19 Risk Communication Package for Healthcare Facilities

TO YOU, OUR HEALTH CARE HEROES, STAY HEALTHY!

MIKE HENNESSY, SR., IS CHAIRMAN AND FOUNDER OF DERMATOLOGY TIMES’ PARENT COMPANY, MJH LIFESCIENCES.
Severe itch can be as debilitating as severe pain.

Innovation in the fight against itch

by BRIAN KIM, M.D., MTR, DUKE LEAHEY, & STEVE, XU M.D., FAAD

Dr. Kim is an associate professor at Washington University School of Medicine; co-director, Center for the Study of Itch and Sensory Disorders; and founder and chief scientific officer, Nuogen Pharma, Inc. His laboratory focuses on innate immune mechanisms that underlie skin inflammation and the sensation of itch. Mr. Leahey is the co-founder of Nuogen Pharma, Inc. He is also the founder of Life Science Alliances, LLC, a consulting company which assists in the formation of science-based companies in the biopharmaceutical and agricultural biotechnology markets. Dr. Xu is an instructor in dermatology at Northwestern University Feinberg School of Medicine; medical director, Center for Bio-Integrated Electronics, Simpson Querrey Institute for Bionanotechnology, Northwestern University; and, co-founder, Advancing Innovation in Dermatology.

We have all been here: A very nice patient sits in the chair. She is desperately trying not to scratch. A stack of papers on the table is filled with laboratory results and urine tests. Next to that is a plastic bag filled topical products that have failed. She’s asking for your help to give her relief. As a dermatologist, these patients break my heart.

Chronic pruritus, defined as itch lasting greater than six weeks, affects approximately 15% of the population and is highly debilitating. Although chronic itch can present in the context of a variety of inflammatory skin disorders, as well as other medical conditions like kidney and liver failure, it commonly arises independently of any defined cause. In this setting, it is referred to as chronic pruritus of unknown origin (CPUO), which accounts for up to 40% of individuals with chronic itch. Strikingly, there are no FDA-approved medications to treat CPUO and most other chronic itch disorders. Thus, there is an urgent need for innovation in this space to develop novel anti-itch therapies.

SPOTLIGHT ON NUOGEN PHARMA

Nuogen Pharma, Inc., is an early stage biopharmaceutical company co-founded by Duke Leahey, CEO, and Brian S. Kim, M.D, CSO, based on key discoveries from Dr. Kim’s laboratory at Washington University School of Medicine in St. Louis. Nuogen Pharma’s mission is to deliver the first FDA-approved anti-itch medication for CPUO and other chronic itch conditions.

Dr. Kim and Mr. Leahey met in 2015 through a mutual colleague who was aware of the high-impact research underway in the Kim Lab. Building upon the discovery that inhibition of Janus kinases in sensory neurons potently treats itch, published in Cell in 2017, a patent was filed for the use of JAK inhibitors for chronic itch.

Leveraging this innovation, Nuogen Pharma was formed in November of 2018 and is working with experienced partners in the pharmaceutical industry to develop novel JAK inhibitors that can be delivered directly to the nervous system via an intranasal route of delivery. This strategy would allow for maximum efficacy of drug while minimizing hematological side effects that are associated with JAK inhibitors.

The vision for Nuogen Pharma is to be an exclusive anti-itch pharmaceutical company that rapidly brings novel technologies to the highly unmet market of chronic itch. Chronic itch is one of the most common symptoms in all of dermatology and medicine. Therefore, Nuogen Pharma’s mission is to bring soothing relief to millions of patients who suffer from this silent epidemic.

Severe itch can be as debilitating as severe pain. There are few conditions in the house of medicine that cause as much patient suffering with so few options. Ongoing development for drugs like difelikefalin, which is being studied for hemodialysis patients with moderate-to-severe pruritus; nemolizumab, which was granted breakthrough therapy status by the FDA for prurigo nodularis; and JAK inhibitors like those being developed by Nuogen Pharma, offer new and much needed therapeutic options for itch.
More treatment options

CHERYL GUTTMAN KRADER, B.S. PHARM | Staff Correspondent

Options for medical acne treatment have expanded significantly since October 2018 with the U.S. Food and Drug Administration (FDA) approval of several novel products, and the future may hold more developments, says Lawrence F. Eichenfield, M.D., who spoke recently at the Maui Derm for Dermatologists 2020 meeting, Maui, Hawaii.

“It has been a busy time in acne drug development leading to the availability of new topical and oral products across the spectrum of medication categories used to treat acne,” says Dr. Eichenfield, professor of dermatology and pediatrics, University of California, San Diego, and chief, pediatric and adolescent dermatology, UCSD/Rady Children’s Hospital, San Diego.

RETINOIDS
Trifarotene cream 0.005% (Aklief, Galderma) is a novel retinoid approved by the FDA in October 2019 for the topical treatment of acne vulgaris in patients aged 9 years and older. Trifarotene is distinguished from tretinoin and adapalene pharmacologically by having >20-fold selectivity for the gamma subtype of the retinoid acid receptor versus RARα and RARβ.

Efficacy and safety of the 0.005% cream formulation were established in two phase 3 studies where it was compared with vehicle for treatment of moderate acne on both the face and the trunk. At the end of the 12-week double-blind treatment period, trifarotene demonstrated statistical superiority to vehicle in all primary and secondary efficacy endpoints that analyzed investigator global assessment and patient global assessment success rates and changes in inflammatory and non-inflammatory lesions.

“Trifarotene is the first topical retinoid studied for treatment of acne on the trunk, an area for which there was historically reluctance to use a topical retinoid due to concerns about lack of efficacy and the potential for excessive systemic exposure,” says Dr. Eichenfield.

“Results from a long-term extension study conducted primarily to evaluate safety showed there was a continuous improvement in the percentage of patients achieving both IGA and PGA success over time. At week 52, 58% of patients achieved overall success defined as achieving both IGA and PGA success, and there was no observed fall of responsiveness over time.”

Topical trifarotene was very well tolerated. Adverse event data showed erythema, scaling, dryness, stinging and burning were generally mild, occurred at low rates and dissipated with ongoing treatment.

Tazarotene lotion 0.045% (Arazlo, Ortho Dermatologics) was approved by the FDA for the treatment of acne vulgaris in patients aged 9 years and older in December 2019. It formulates the retinoid in a novel vehicle at a lower concentration compared with the gel product that is approved for acne.

“Tazarotene is a very potent topical retinoid, but it has been used inconsistently for the treatment of acne because it can be quite irritating,” says Dr. Eichenfield.

“The lotion formulation of tazarotene is a polymeric emulsion technology in which the active and emollient ingredients form an oil-in-water emulsion that is structured by a three-dimensional mesh matrix. The technology enables rapid and even ingredient release.”

The phase 3 studies of the new tazarotene product enrolled patients with moderate or severe acne aged 9 years and older. The results showed statistically significant differences favoring the tazarotene lotion versus vehicle at week 12 in the percentage of patients achieving a two-grade improvement from baseline with a rating of clear or almost clear disease and in analyses of percent change in both inflammatory and non-inflammatory lesions.

Severity of scaling, erythema, itching, burning and stinging were rated on a scale of 0 (none) to 3 (severe) and the mean scores for all of those adverse events were close to 0.

ANTIBIOTIC ALTERNATIVES
Recently approved antibiotics for the treatment of acne include both topical and oral products. The efficacy and safety of minocycline foam 4% (Amzeeq, Foamix), which was approved for the treatment of inflammatory lesions of non-nodular moderate-to-severe acne vulgaris in October 2019, was investigated after extensive dermal safety studies were completed that showed no evidence of phototoxicity, photoallergy, skin sensitization, or clinically significant cumulative skin irritation. In addition, a pharmacokinetics study was done that showed very low systemic absorption with topical application for 21 days.

The phase 3 studies enrolled patients aged 9 years and older with moderate-to-severe acne who were randomized to once daily treatment with vehicle or minocycline foam 4%. They met their co-primary efficacy endpoint that analyzed IGA treatment success and absolute change from baseline in inflammatory lesion count at week 12.

In addition, a subgroup analysis of data from three randomized, double-blind phase 3 studies showed that the efficacy of minocycline foam 4% in pediatric patients (ages 9 to 17 years) was similar to that seen in the overall study population. An open-label pediatric study investigating treatment under maximum-use conditions showed...
Not only does the use of oral antibiotics for treatment of acne increase antibiotic resistance of Cutibacterium acnes that is involved in acne pathogenesis, but it also increases resistance of other commensal and opportunistic bacteria that colonize the skin and other tissues.”

James Q. Del Rosso, M.D., Touro University Nevada, Henderson, Nev.

With the aim of reducing the risk for antibiotic resistance, acne treatment guidelines generally recommend that oral antibiotics not be given for longer than three to six months. Hopefully, the patient’s acne will have improved enough to allow discontinuation of the antibiotic, and, if not, an alternative therapy can be considered. In the real world; however, some patients may require a longer course of antibiotics because they are not a candidate for alternatives or for retreatment of worsening or recurring acne in the future.

“So, the cycle of antibiotic use often continues as the goal of the clinician for their patient, including myself, is to keep the acne as clear as possible,” Dr. Del Rosso says.

Considering these scenarios, Dr. Del Rosso emphasized the need to have an “exit plan” when initiating oral antibiotic treatment for acne and counseling patients up front of its intent.

“The literature and guidelines often try to set some hard and fast rules about duration of oral antibiotic use, but they are not based on hard scientific evidence regarding duration of use, and clinicians always need to use their judgment to optimize treatment for individuals,” Dr. Del Rosso says.

“Nevertheless, clinicians need to be aware of the potential for promoting resistance with long-term antibiotic treatment so that they use antibiotics responsibly and prepare patients from the outset for the possibility of using other options to manage their acne, which can also be considered up front in acne management.”

Sarecycline (Seysara, Almirall), a new tetracycline-class antibiotic approved for treating moderate-to-severe acne patients aged ≥ 9 years, may potentially cause less bacterial resistance than older tetracyclines because it has a narrower antimicrobial spectrum with less activity against enteric Gram-negative bacteria.

“Whether the narrower antibacterial spectrum of sarecycline will be relevant clinically in terms of causing less disruption to the commensal flora and less antimicrobial resistance remains to be seen. However, there are some data to support this differentiation of sarecycline as a narrow spectrum tetracycline. Based on clinical trial data, sarecycline does exhibit very low rates of gastrointestinal upset, dizziness, photosensitivity and vaginal candidiasis,” Dr. Del Rosso says.

**Quick Takes**

Antibiotic prescribing for acne should take into account the potential for promoting bacterial resistance.

Sarecycline potentially may be less likely than older tetracyclines to promote resistance emergence among enteric Gram-negative bacteria because it has a narrower antimicrobial spectrum. Further studies are needed in this area.

Lidose-isotretinoin taken without food was associated with a relatively low long-term relapse rate in a 2-year phase 4 study, which is consistent with knowledge about its bioavailability and the association between early relapse and cumulative systemic isotretinoin exposure.

New evidence suggests that some laboratory monitoring may not be needed routine in patients being treated with isotretinoin or spironolactone, but decisions for follow-up and laboratory testing are best individualized.

**Antibiotic Therapy Update**

CHERYL GUTTMAN KRADER, B.S. PHARM | Staff Correspondent

Findings from recent research and new product developments have implications for addressing some of the challenges that can accompany the use of oral therapies for acne, says James Q. Del Rosso, D.O., who discussed antibiotic resistance, isotretinoin relapse, and laboratory monitoring for patients on isotretinoin and spironolactone at the 18th annual South Beach Symposium in February in Miami.

A rational combination topical regimen along with an oral antibiotic are often recommended for treatment of moderate-to-severe acne, but the potential for antibiotic resistance supports efforts to limit the duration of antibiotic exposure.

“Not only does the use of oral antibiotics for treatment of acne increase antibiotic resistance of Cutibacterium acnes that is involved in acne pathogenesis, but it also increases resistance of other commensal and opportunistic bacteria that colonize the skin and other tissues,” says Dr. Del Rosso, research director, JDR Dermatology Research, Las Vegas, and adjunct clinical professor of dermatology, Touro University Nevada, Henderson, Nev.

With the aim of reducing the risk for antibiotic resistance, acne treatment guidelines generally recommend that oral antibiotics not be given for longer than three to six months. Hopefully, the patient’s acne will have improved enough to allow discontinuation of the antibiotic, and, if not, an alternative therapy can be considered. In the real world; however, some patients may require a longer course of antibiotics because they are not a candidate for alternatives or for retreatment of worsening or recurring acne in the future.

“So, the cycle of antibiotic use often continues as the goal of the clinician for their patient, including myself, is to keep the acne as clear as possible,” Dr. Del Rosso says.

Considering these scenarios, Dr. Del Rosso emphasized the need to have an “exit plan” when initiating oral antibiotic treatment for acne and counseling patients up front of its intent.

“The literature and guidelines often try to set some hard and fast rules about duration of oral antibiotic use, but they are not based on hard scientific evidence regarding duration of use, and clinicians always need to use their judgment to optimize treatment for individuals,” Dr. Del Rosso says.

“Nevertheless, clinicians need to be aware of the potential for promoting resistance with long-term antibiotic treatment so that they use antibiotics responsibly and prepare patients from the outset for the possibility of using other options to manage their acne, which can also be considered up front in acne management.”

Sarecycline (Seysara, Almirall), a new tetracycline-class antibiotic approved for treating moderate-to-severe acne patients aged ≥ 9 years, may potentially cause less bacterial resistance than older tetracyclines because it has a narrower antimicrobial spectrum with less activity against enteric Gram-negative bacteria.

“Whether the narrower antibacterial spectrum of sarecycline will be relevant clinically in terms of causing less disruption to the commensal flora and less antimicrobial resistance remains to be seen. However, there are some data to support this differentiation of sarecycline as a narrow spectrum tetracycline. Based on clinical trial data, sarecycline does exhibit very low rates of gastrointestinal upset, dizziness, photosensitivity and vaginal candidiasis,” Dr. Del Rosso says.
that minocycline foam 4% was generally safe, well-tolerated and associated with low minocy-
cline systemic exposure.

Sarecycline (Seyara, Almirall) is an oral tetr-
cycline-derived antibiotic approved in October 2018 for once daily treatment of moderate-to-se-
vere acne vulgaris in patients aged 9 years and older. Dosing is determined by patient weight and
the clinical trials showed efficacy for treat-
ing both facial and truncal acne.

“In addition to its once daily dosing, sarecy-
cline is distinguished from other tetracyclines
by having minimal impact on Gram-negative enteric bacteria, although whether that differ-
ence has clinically relevant implications remains
to be seen,” says Dr. Eichenfield.

AWAITING APPROVAL

The New Drug Application for clascoterone cream 1% (Winlevi, Cassiopea) as a treatment for acne is undergoing FDA review. Its mecha-
nism of action for acne treatment is thought to be competitive inhibition of dihydrotestoster-
one binding to androgen receptors within sebo-
cyes and hair papilla cells.

Topline results from the phase 3 studies
enrolling patients with moderate-to-severe facial
acne aged 9 years and older show the primary
endpoints were met. Data from a long-term exten-
sion study showed that after 9 months, approxi-
cately 30% of patients achieved clear or almost
clear ratings. Erythema and scaling, which
tended to decrease over time, were the most com-
mon side effects.

“Importantly, there was no evidence of
adverse effects on hair production and no evi-
dence of absorption resulting in systemic hor-
monal effects,” says Dr. Eichenfield.

MORE UPDATES

Dr. Eichenfield also reminded attendees about
the publication of evidence-based recomenda-
tions for the management of spontaneous and
isotretinoin-induced acne fulminans.

“There is limited data in the literature from
prospective studies on this severe variant of
inflammatory acne, and there have not been any
clear guidelines about its treatment,” he says.

“These guidelines were developed based on
a systematic literature review and expert consen-
sus to help practitioners classify acne fulminans
and to treat it with oral steroids and isotretinoin
when appropriate.”

Looking ahead, ongoing research focusing on
the pathophysiology importance of differ-
ent strains of Cutibacterium acnes and Staphylo-
coccus epidermidis may lead to new skin micro-
biome-based treatments for acne, including vac-
cines. New insights on acne pathogenesis that
may identify future therapeutic targets may also
come from research that is analyzing cytokine
gene expression profiles.

Disclosure:

Dr. Eichen/f_eld is an investigator and/or consultant for Allergan, Almirall, Cassio-
pea, Foamx, Galderma, L’Oreal, and Orto/Dermatologics.

Reference:


RELAPSE RISK

While many patients with severe acne who
receive a course of isotretinoin are able to
remain clear or dramatically clear for months
to years after stopping the drug, early relapses
do occur.

The risk for these events depends on cumula-
tive systemic exposure to isotretinoin, which may
have been reduced in many patients who likely
did not ingest their medication with a high-fat/
high-calorie meal.

“According to pharmacokinetic data, optimal
absorption of traditional isotretinoin requires
that each dose be taken with a 50-g fat/1000-cal-
orie meal. It is expected that the vast majority
of people do not meet those dietary levels in the real
world, and some patients may take their medica-
tion without any food,” Dr. Del Rosso says.

Isotretinoin absorption with lidose-isotreti-
noin (Absorica, Sun Pharmaceuticals) is less
dependent on food because the active ingredient
is pre-solubilized in a lipid matrix. Therefore, it
depends on food because the active ingredient
is less

“Therefore, clinicians should decide based
on their own comfort level whether they want
to limit potassium monitoring to specific indi-
viduals or continue with baseline and fol-
low-up testing for all patients being treated with
spironolactone.”

He added that spironolactone should not be
prescribed to patients taking lithium due to high
risk of inducing lithium toxicity.

Disclosure:

Dr. Del Rosso is a research investigator, consultant/advisor, and speaker for Aller-
gan and Sun Pharmaceuticals and a research investigator, consultant/advisor,
and/or speaker for many other companies that manufacture or are developing products
for treatment of acne.

References

1. Del Rosso JG, Shen GD, Segal J, Zangwil AL, Ancopen label; phase II
   study evaluating lidose-isotretinoin monotherapy without food in patients with
2. Lee HY, Schramm TM, Maciej J, et al. Laboratory monitoring during isotreti-
3. Thiede RM, Stroff K, Nordenstam E, et al. Hyperkalemia in women who are
   exposed to spironolactone. A prospective study from the RADAR (Research
4. Piacquadio DJ, Worley D. Low awareness of potassium monitoring
Pivotal trials positive

CHERYL GUTTMAN KRADER, B.S. PHARM | Staff Correspondent

Despite being a molecule that is very difficult to formulate topically, Minocycline foam is a novel topical formulation developed for the treatment of papulopustular rosacea in adults.

Published results from two 12-week, vehicle-controlled phase 3 studies show that FMX103 met its co-primary efficacy endpoints for reducing inflammatory lesions and achieving Investigator’s Global Assessment treatment success.

Safety and tolerability results were favorable.

More than 95% of patients using FMX103 reported no or mild skin tolerability issues.

95%

patients using FMX103 reported no or mild skin tolerability issues

T
reatment with an oral tetracycline is commonly used for patients with moderate-to-severe papulopustular rosacea (PPR), and while it can be very effective for reducing these inflammatory lesions, the potential side effects of oral tetracyclines can be bothersome if not treatment limiting.

The phase 3 clinical trial program was undertaken after results of a large phase 2 study showed that patients treated with FMX103 for 12 weeks had statistically significant reduction from baseline in inflammatory lesion count and improvement in Investigator’s Global Assessment scores. The two phase 3 studies had an identical design. Both were multicenter, double-blind trials randomizing patients 2:1 to use of FMX103 or vehicle once daily for 12 weeks.

Eligible patients were aged ≥18 years with an IGA score of 3 (moderate) or 4 (severe) with between 15 and 75 facial papules and/or pustules and no more than 2 facial nodules. They were also required to have a history of or current facial erythema and/or flushing. Patients with moderate or severe rhinophyma, dense telangiectasia, or plaque-like facial edema were excluded.

Patients were instructed to apply their assigned treatment as a thin layer over the entire face and to treat as a daily ordeal. A total of 1,521 patients were enrolled in the two phase 3 studies, of which 1,008 received at least one dose of FMX103. The active treatment groups in the two studies versus in 0.0% and 0.4% of patients in the vehicle groups. Pruritus was the most commonly reported adverse event, occurring in 0.2% of patients using FMX103 who were rated as clear or almost clear for erythema increased from baseline to week 12 in both studies, rising from 4.3% to 6.6% in one trial and from 3.4% to 4.8% in the other study.

There were no serious treatment-related adverse events nor any cutaneous adverse events that occurred at a rate ≥2% in either treatment group. Pruritus was the most commonly reported cutaneous adverse event, occurring in 0.8% and 0.6% of patients in the FMX103 treatment groups in the two studies versus 0.0% and 0.4% of patients in the vehicle groups.

More than 95% of patients using FMX103 reported no or only mild skin tolerability issues," Dr. Stein Gold says. ▶

Disclosure: Dr. Stein Gold is an investigator for Forma, Galderma, Leo Pharma, Novartis, and Valeant; an investigator for Janssen, AbbVie, and Solgel.
Combination strategies

CHERYL GUTTMAN KRADER, B.S. PHARM | Staff Correspondent

Outcomes achieved with combination pharmacotherapy regimens and investigational agents make this an exciting time for rosacea management, Linda Stein Gold, M.D., told colleagues during the January Orlando Dermatology Aesthetic & Clinical conference, Orlando, Fla.

“Combination strategies can address both inflammatory lesions and background erythema for patients with rosacea with benefits of faster onset of improvement and higher clearance rates that can translate into longer lasting remissions once treatment is stopped,” says Dr. Stein Gold, director of clinical research, department of dermatology, Henry Ford Hospital, Detroit. “Novel topical formulations of minocycline and benzoyl peroxide (BPO) have already completed pivotal trials where they demonstrated efficacy and favorable safety in patients with moderate-to-severe papulopustular rosacea (PPR).”

DYNAMIC DUOS
Recent studies have reported the results from combination regimens using ivermectin cream, 1% (Soolantra, Galderma) with either brimonidine gel, 0.33% (Mirvaso, Galderma) or sub-microbial dose doxycycline (Oraeca, Galderma).1,2

The combination topical therapy approach was investigated in a multicenter, randomized, double-blind, vehicle-controlled study in which 190 patients with moderate-to-severe PPR and marked persistent facial erythema were assigned 1:1:2 to use brimonidine gel in the morning plus ivermectin cream in the evening for 12 weeks, brimonidine vehicle in the morning plus ivermectin in the evening for four weeks followed by once-daily treatment with both active agents for eight weeks, or the vehicles of both agents once daily for the entire 12-week study.1 Use of the ivermectin and brimonidine for 12 weeks was associated with the greatest benefit; at 12 weeks, 55.8% of patients in that group achieved an Investigator’s Global Assessment (IGA) rating of “clear” or “almost clear” for facial erythema and PP lesions.

The addition of low-dose oral doxycycline (40 mg/day) to topical ivermectin was shown to accelerate and increase response rates compared with the topical treatment alone in a multicenter randomized, investigator-blinded 12-week trial enrolling patients with severe rosacea (IGA score of 4).2 Both study groups benefited with marked reductions in inflammatory lesion counts by week four and showed ongoing improvement over the duration of the study. Already by week four, however, the mean percentage reduction of inflammatory lesions from baseline was significantly greater in the combination group than for patients using ivermectin alone (48.15% vs. 39.27%; P = .007). The dual regimen maintained statistically significant superiority at weeks eight and 12. In addition, the percentage of patients achieving 100% clearance of inflammatory lesions at week 12 was 2.5-fold greater in the combination group compared with the controls using ivermectin alone, and the difference was statistically significant (17.8% vs. 7.2%; P = .006).

“Combination strategies can address both inflammatory lesions and background erythema for patients with rosacea with benefits of faster onset of improvement and higher clearance rates.” Linda Stein Gold, M.D. Henry Ford Hospital, Detroit

ON THE HORIZON
The pipeline of products for rosacea includes two topical agents that have completed phase 3 trials.3,4 FMX103 (Foamix Pharmaceuticals), a foam formulation of minocycline 1.5%, was investigated in two phase 3 studies enrolling more than 1,500 patients who were randomized 2:1 to treatment with the minocycline product or vehicle foam.

Read more about this study on page 15.

“Topical application of minocycline offers the potential to reduce the risk of systemic adverse events, but minocycline is a large molecule that has been challenging to deliver topically and challenging to incorporate in a stable, cosmetically acceptable vehicle,” says Dr. Stein Gold.

“This topical formulation achieves very high concentrations in the skin with negligible plasma levels, and shows promise for being a useful new treatment option,” Dr. Stein Gold says.

Formulation scientists have also overcome the challenge of using topical BPO to treat rosacea by using silica-based micro-encapsulated technology for modified release of the active ingredient. “With this preparation, however, BPO achieves a concentration on the skin exceeding the threshold for efficacy but remaining below the level that would induce adverse events,” she explains.

Results of two phase 3 studies showed that a novel cream formulation containing 5% micro-encapsulated BPO (Epsolay, Sol-Gel Technologies) was very effective and very well-tolerated as a treatment for moderate-to-severe rosacea.1 In both studies, the percentage of patients achieving IGA ratings of 0 or 1 was significantly greater (P < .001) in the BPO group than in the vehicle-treated controls by week four, and the differences between groups widened after four and eight weeks and were maintained at the end of the 12-week studies. The percentages of patients reporting any itching or any burning/stinging decreased from baseline to week 12 in all study groups, but the reductions seen in the BPO groups were similar to or exceeded those observed in the vehicle-treated patients.

Disclosure:
Dr. Gold is a consultant, investigator, and/or speaker for Galderma, Foamix, and other companies that market or are developing products for the treatment of rosacea.

References
Addressing the Challenges of Managing Atopic Dermatitis

The overall burden of atopic dermatitis

Atopic dermatitis is such a typical pediatric condition that doctors often make misdiagnoses, yet so uncommon among adults that diagnosis and treatment can be impeded by misconceptions of onset and recurrence.

In this Dermatology Times® podcast, Jonathan Silverberg, MD, PhD, MPH, discusses trends and geographic distribution of the condition’s prevalence, realistic expectations for persistence beyond childhood, and effective differential diagnosis for adult patients.

Listen Now:
www.dermatologytimes.com/atopicdermatitis
and symptoms and then building a therapeutic regimen that addresses the full spectrum of clinical manifestations, according to Julie C. Harper, M.D.

“We are looking at rosacea patients differently today than in the past when the tendency was to pigeonhole people into subtypes . . . and then choose treatment.”

Julie C. Harper, M.D., Birmingham, Ala.

Optimal management is aim of awareness month

An increase in patients seeking care for rosacea may occur as a result of public education efforts during Rosacea Awareness Month.

Treatment for rosacea should be tailored to address all presenting features and may require a multimodal regimen.

EMERGING ADVANCES

New treatments for rosacea are on the horizon with two products having completed phase 3 studies with positive results. They include a topical minocycline product containing 1.5% of the active ingredient in a foam formulation (FMX103) and a cream formulation of microencapsulated benzoyl peroxide 5%. The New Drug Application (NDA) for the minocycline foam is under FDA review and the company developing the benzoyl peroxide product is expected to submit the NDA in the first half of 2020. Both products are targeting approval for treatment of papulopustular rosacea.

Dr. Harper notes that although these two products would not bring an advantage for addressing a broader number of rosacea-related features compared with existing treatments, they will be welcome additions because they will give clinicians a greater number of options, Dr. Harper says.

“We now have several very good products for treating rosacea, but unlike in acne, our choices do not respond adequately after trying a first- and second-line, we may be left with no alternative,” she explains.

“With more therapeutic choices we have more opportunity to help more patients, and that is exciting.”

Patient Education

Considering that rosacea is a chronic and recurrent disease that can be affected by a variety of exogenous triggers, it is especially important that patients become partners in their care. Achieving their participation requires that they understand the nature of their disease along with the role of lifestyle interventions, medications, and proper skin care in its management.

The National Rosacea Society is a rich source for patient education materials that address these issues with accurate and reliable information, said Dr. Harper.

The resources include the Recognizing Redness booklet that was released in 2019. It helps patients identify facial redness related to rosacea, distinguish between baseline redness and a flare-up of their disease, and gauge objectively the effects of treatment being used to control redness.

Other materials include the Coping with Rosacea brochure that discusses trigger avoidance and the psychosocial sequela of rosacea along with other topics, the Rosacea Diary booklet for helping patients to recognize and avoid factors that trigger flares, and the Managing Rosacea brochure that delves into treatment options, lifestyle management, and tips for personal care.

Patients can also be directed to the National Rosacea Society website (rosacea.org) where they can access a wealth of information and download a PDF version of all of those educational materials.
New ways to tackle itch

LISETTE HILTON | Staff Correspondent

Traditional treatments for calming the often intense pruritus that accompanies atopic dermatitis might not be optimal, according to a review published August 2019 in the *Journal of Allergy and Clinical Immunology.*

“Classically, it was widely believed that treatment of atopic dermatitis with anti-inflammatory agents was the only manner in which itch could be alleviated. In other words, inflammation in the skin was inextricably linked to itch. This article highlights new and emerging pathways in atopic dermatitis-associated itch, such that itch can be selectively and potently targeted with newer therapeutics. These include existing therapies like dupilumab (Dupixent, Sanofi and Regeneron Pharmaceuticals), or emerging therapies like [interleukin-] IL-13 and IL-31 antagonists, as well as [Janus kinase] JAK inhibitors,” says review author Brian S. Kim, M.D., MTR, associate professor dermatology and co-director, Center for the Study of Itch, Washington University School of Medicine, in St. Louis.

Researchers have thought itch mechanisms revolved around the canonical IgE-mast-cell-histamine axis, yet therapies focused on blocking the histaminergic itch pathway have been in large part ineffective against atopic dermatitis-associated itch, the authors write. “Today, there’s new emphasis on targeting nonhistaminergic itch pathways.”

Atopic dermatitis patients exhibit systemic immune dysregulation and increased serum IgE levels. Like other atopic disorders, such as asthma and food allergy, atopic dermatitis is associated with increased expression of epithelial cell-derived cytokines, as well as enhanced adaptive TH2 cell and innate basophil, eosinophil, mast cell and group 2 innate lymphoid cell responses, the authors write. These processes, which increase production of effect cytokines IL-4, IL-5 and IL-13, set the stage for the allergic cutaneous immune atopic dermatitis response.

Recent studies point to the immune system interacting with the sensory nervous system to arouse itch. So, researchers are studying things like the effects of H4 antihistamines to treat the itch of atopic dermatitis, according to the authors. “Notwithstanding this, the first cytokine to be identified as a pruritogen was found to be produced by TH2 cells in the context of atopic dermatitis, namely IL-31,” they write.

A phase 2b randomized study published in August in the *Journal of Allergy and Clinical Immunology* of nemolizumab treatment in adults with moderate-to-severe atopic dermatitis and severe pruritus found nemolizumab treatment resulted in rapid and sustained improvements in cutaneous signs of inflammation and pruritus, with an acceptable safety profile.

Dr. Kim and colleagues “recently identified that IL-4 receptor alpha is expressed on sensory neurons and critically regulates itch responses in vivo in a murine model of AD-like disease,” according to the authors. It seems IL-4 and IL-13 promote neuronal hypersensitivity to pruritogens, therefore regulating itch, they write.

While IL-4 is the target of dupilumab, research is underway for anti-IL-13 drugs. Among those: tralokinumab and lebrikizumab. Tralokinumab has significantly improved itch related to atopic dermatitis in trials, according to the paper.

In a review published August 2019 in the *Journal Pediatric Drugs,* the authors report: While the aryl hydrocarbon receptor modulating agent tapinarof, the IL-4/IL-13 antagonists lebrikizumab and tralokinumab, and the IL-31Ra antagonist nemolizumab have potential in atopic dermatitis treatment, Janus Kinase (JAK)-STAT inhibitors (baricitinib, upadacitinib, PF-04965842, ASN002, tofacitinib, ruxolitinib and delgocitinib) have the most promise among emerging therapies.

Dr. Kim and colleagues write they have in recent studies identified neuronal JAK1 signaling as an important regulator of atopic dermatitis itch in vivo and JAK inhibitors probably have neuromodulatory properties.

**References online:** bit.ly/itchtreatment


4 Dr. Kim has served as a consultant to AbbVie, Case Therapeutics, Concert Pharmaceuticals, Incyte, Menlo Therapeutics, and Pfizer. He has served on advisory boards for Galgina, K他人 Pharmaceutical, Menlo Therapeutics, Regeneron Pharmaceuticals, Sanofi, and Thea Pharma, and is a founder, chief scientific officer and stockholder of Naugur Pharma.
Indication and Usage

Enstilar® (calcipotriene and betamethasone dipropionate) Foam is indicated for the topical treatment of plaque psoriasis in patients 12 years and older. Apply Enstilar Foam to affected areas once daily for up to 4 weeks. Discontinue use when control is achieved. Instruct patients not to use more than 60 grams every 4 days.

Important Safety Information

For topical use only. Enstilar Foam is not for oral, ophthalmic or intravaginal use and should not be applied on the face, groin or axillae or if skin atrophy is present at the treatment site. Do not use with occlusive dressings. Patients should wash hands after application.

Please see Brief Summary of Prescribing Information on following page.

Most commercially insured patients pay as little as $20*

An experience worth noticing.

With clinical efficacy and safety profile in a once-daily spray foam, choose the Enstilar® Foam experience for your patients with plaque psoriasis.†

In adults, patients achieved "Clear" or "Almost Clear" skin as measured by IGA1,2:

- 53.3% vs 4.8% for vehicle at Week 4 (P<0.001)
- 26.4% vs 1.9% for vehicle at Week 2

†Valid for up to 12 prescription fills per calendar year. Patients are not eligible if they are enrolled in or eligible for any state or federally funded health care programs (e.g., Medicare, Medicaid). Additional restrictions and limitations apply. See www.leopharmaconnect.com.

- A randomized clinical trial with 426 patients, ≥18 years of age, that investigated the effectiveness of Enstilar® or the vehicle alone for the treatment of psoriasis vulgaris on the trunk and/or limbs. Efficacy was assessed using a 5-point IGA at Week 4, with treatment success defined as the percentage of patients who achieved at least a 2-step improvement to reach "Clear" or "Almost Clear" disease severity. Patients with "Mild" disease were required to be "Clear" to be considered a treatment success.1,2

IGA=Investigator’s Global Assessment.

Not an actual patient. Image is a representation of plaque psoriasis. Individual results may vary.

ENSTILAR® (calcipotriene and betamethasone dipropionate) foam, for topical use

Rx Only

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

INDICATIONS AND USAGE
Enstilar® (calcipotriene and betamethasone dipropionate) Foam is indicated for the topical treatment of plaque psoriasis in patients 12 years and older.

DOSEAGE AND ADMINISTRATION
Instruct patients to shake can prior to using Enstilar Foam and to wash their hands after application. Apply Enstilar Foam to affected areas once daily for up to 4 weeks. Riu in Enstilar Foam is 15g (420mg of calcipotriene and 1140mg of betamethasone dipropionate). Discontinue Enstilar Foam when control is achieved. Patients should not use more than 60 grams every 4 days.

Enstilar Foam should not be:
- Used with occlusive dressings unless directed by a healthcare provider.
- Used on the face, groin, or axillae, or if skin atrophy is present at the treatment site.

Dosage Forms and Strengths
Enstilar Foam: 0.005%/0.004% - each gram contains 50 mcg calcipotriene and 0.643 mcg of betamethasone dipropionate in a white to off-white opalescent liquid in a pressurized aluminum spray can with a continuous valve and actuator. At administration the product is a white to off-white foam after evaporation of the propellants.

CONTRAINDICATIONS.
None.

WARNINGS AND PRECAUTIONS
Flammability
The propellants in Enstilar Foam are flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application.

Hypercalcemia and Hypercalciuria
Hypercalcemia and hypercalciuria have been observed with use of Enstilar Foam. If hypercalcemia or hypercalciuria develop, discontinue treatment until parameters of calcium metabolism have normalized. The incidence of hypercalcemia and hypercalciuria following Enstilar Foam treatment of more than 4 weeks has not been evaluated.

Effects on Endocrine System
Hypothalamic-Pituitary-Adrenal Axis Suppression
Systemic absorption of topical corticosteroids can cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment. Factors that predispose a patient to HPA axis suppression include the use of high-potency steroids, large treatment surface areas, prolonged use of occlusive dressings, altered skin barrier, liver failure, and young age.

Evaluation for HPA axis suppression may be done by using the adrenocorticotropic hormone (ACTH) stimulation test. If HPA axis suppression is documented, gradually withdraw Enstilar Foam, reduce the frequency of administration, or substitute with a less potent corticosteroid.

The following trials evaluated the effects of Enstilar Foam on HPA axis suppression:
- In a trial evaluating the effects of Enstilar Foam on the HPA axis, 35 adult subjects applied Enstilar Foam on the body and scalp. Adrenal suppression was not observed in any subjects after 4 weeks of treatment. In another trial, 33 pediatric subjects aged 12 to 17 years applied Enstilar Foam on the body and scalp. Adrenal suppression occurred in 3 (9%) of the subjects.
- Cushing’s Syndrome and Hyperglycemia
Systemic effects of topical corticosteroids may also include Cushing’s syndrome, hyperglycemia, and glucosuria.

Additional Considerations for Endocrine Adverse Reactions
Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios.

Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure.

Allergic Contact Dermatitis
Allergic contact dermatitis has been observed with topical calcipotriene and topical corticosteroids. Allergic contact dermatitis to a topical corticosteroid is usually diagnosed by observing a failure to heal rather than a clinical exacerbation. Corroborate such an observation with appropriate diagnostic patch testing.

Ophthalmic Adverse Reactions
Use of topical corticosteroids, including Enstilar® Foam, may increase the risk of posterior subcapsular cataracts and glaucoma. Cataracts and glaucoma have been reported with the use of topically applied corticosteroids. Avoid contact with Enstilar Foam with eyes. Enstilar Foam may cause eye irritation. Advise patients to report any visual symptoms and consider referral to an ophthalmologist for evaluation.

ADVERSE REACTIONS
Clinical Trials in General
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 practice.

Clinical Trials Conducted in Subjects 18 years and older with Psoriasis
The rates of adverse reactions described below were from three randomized, multicenter, vehicle and/or active-controlled clinical trials in adult subjects with plaque psoriasis.

Subjects applied study product once daily for 4 weeks, and the median weekly dose of Enstilar Foam was 5.5 grams. Adverse reactions reported in <1% of pediatric subjects treated were acne, erythema, application site pain, and skin reactions.

Postmarketing Experience
Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Postmarketing reports for local adverse reactions to topical corticosteroids included atrophy, striae, telangiectasia, dryness, perioral dermatitis, secondary infection, and miliania. Ophthalmic adverse reactions of cataracts, glaucoma, increased intraocular pressure, and central serous choroidopathy have been reported with the use of topically applied corticosteroids, including topically applied betamethasone products.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
Available data with Enstilar Foam are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriages, or adverse maternal or fetal outcomes. Although there are no available data on use of the calcipotriene component in pregnant women, systemic exposure to calcipotriene following topical administration of Enstilar Foam is likely to be low.

Observational studies suggest an increased risk of having low birth weight infants with the maternal use of potent or super potent topical corticosteroids. Advise pregnant women who use Enstilar Foam during pregnancy that this drug can cause fetal harm when administered to pregnant rats. Advise pregnant women not to use Enstilar Foam on the smallest area of skin and for the shortest duration possible.

In animal reproduction studies, oral administration of calcipotriene to pregnant rats during the period of organogenesis resulted in an increased incidence of minor skeletal abnormalities, including enlarged fontanelles and extra ribs. Oral administration of calcipotriene to pregnant rabbits during the period of organogenesis had no apparent effects on embryo-fetal development. Subcutaneous administration of betamethasone dipropionate to pregnant rats and rabbits during the period of organogenesis resulted in fetal toxicity, including fetal deaths, reduced fetal weight, and fetal malformations (cleft palate and crooked or short tail). The available data do not allow the calculation of relevant comparisons between the systemic exposures of calcipotriene and betamethasone dipropionate observed in animal studies to the systemic exposures that would be expected in humans after topical use of Enstilar® Foam. The estimated background risk of major birth defects and miscarriage of the indicated population is unknown. All pregnancies have a background risk of fetal defect, loss, or 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% to 4% and 15% to 20%, respectively.

Data
Human Data
Available observational studies in pregnant women did not identify a drug-associated risk of major birth defects, preterm delivery, or fetal mortality with the use of topical corticosteroids of any potency. However, when the dispensed amount of potent or super potent topical corticosteroids exceeded 300 grams during the entire pregnancy, maternal use was associated with an increased risk of low birth weight in infants.

Animal Data
Embryo-fetal development studies with calcipotriene were performed by the oral route in rats and rabbits. Pregnant rats received doses of 0, 6, 18, or 54 mcg/kg/day (0, 36, 108, and 324 mcg/m²/day, respectively) on days 6-15 of gestation (the period of organogenesis). There were no apparent effects on maternal survival, behavior, or body weight gain, no effect on litter parameters, and no effects on the incidence of major malformations. Fetuses from dams dosed at 54 mcg/m²/day exhibited a significantly increased incidence of minor skeletal abnormalities, including enlarged fontanelles and extra ribs. Pregnant rabbits were dosed daily with calcipotriene at exposures of 0, 4, 12, or 36 mcg/kg/day (0, 48, 144, and 432 mcg/m²/day, respectively) on days 6-18 of gestation (the period of organogenesis). Mean maternal body weight gain was reduced in animals dosed at 12 or 36 mcg/kg/day. The incidence of fetal deaths was increased in the group dosed at 36 mcg/kg/day, reduced fetal weight was also observed in this group. The incidence of major malformations among fetuses was not affected. An increase in the incidence of minor skeletal abnormalities, including incomplete ossification of sternebrae, pubis bones, and forelimb phalanges, was observed in the group dosed at 36 mcg/kg/day.

Embryo-fetal development studies with betamethasone dipropionate were performed via subcutaneous injection in mice and rabbits. Pregnant mice were administered doses of 0, 156, 625, or 2500 mcg/kg/day (0, 468, 1875, and 7500 mcg/m²/day, respectively) on days 7 through 13 of gestation (the period of organogenesis). Betamethasone dipropionate induced fetal toxicity, including fetal deaths, reduced fetal weight, and fetal malformations (increased incidence of the cleft palate and crooked or short tail), and minor skeletal abnormalities (delayed ossification of vertebrae and sternum). Fetal toxicity was observed at the lowest exposure that was evaluated (156 mcg/kg/day).

Pregnant rabbits were injected subcutaneously at doses of 0, 625, 2.5, and 10 mcg/kg/day (0, 7.5, 30, and 120 mcg/m²/day, respectively) on days 6 through 18 of gestation (the period of organogenesis). Betamethasone dipropionate induced fetal toxicity, including fetal deaths, reduced fetal weight, external malformations (cleft palate, umbilical hernia, kinked tail, club foot, and club hands), and skeletal malformations (including absence of phalanges of the first digit and cranial dysplasia) at doses of 2.5 mcg/kg/day and above.

Calcipotriene was evaluated for effects on peri- and postnatal development when orally administered to pregnant rats at doses of 0, 6, 18 or 54 mcg/kg/day (0, 36, 108, and 324 mcg/m²/day, respectively) from gestation day 15 through day 20 postpartum. No remarkable effects were observed on any parameter, including survival, behavior, body weight, litter parameters, or the ability to nurse or rear pups.
Betamethasone dipropionate was evaluated for effects on peri- and post-natal development when orally administered to pregnant rats at dosages of 0, 100, 300, and 1000 mcg/kg/day (0, 600, 1800, and 6000 mcg/m²/day, respectively) from gestation day 6 through day 20 postpartum. Mean maternal body weight was significantly reduced on gestation day 20 in animals dosed at 300 and 1000 mcg/kg/day. The mean duration of gestation was slightly, but statistically significantly, increased at 100, 300, and 1000 mcg/kg/day. The mean percentage of pups that survived to day 4 was reduced in relation to dosage. At postpartum day 5, the percentage of pups with a reflex to right themselves when placed on their back was significantly reduced at 1000 mcg/kg/day. No effects on the ability of pups to learn were observed, and the ability of the offspring of treated rats to reproduce was not affected.

**Lactation**

**Risk Summary**

There is no information regarding the presence of topically administered calcipotriene and betamethasone dipropionate in human milk, the effects on the breastfed infant, or the effects on milk production. Concentrations of calcipotriene in plasma are low after topical administration, and therefore, concentrations in human milk are likely to be low. It is not known whether topical administration of large amounts of betamethasone dipropionate could result in sufficient systemic absorption to produce detectable quantities in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Enstilar® Foam and any potential adverse effects on the breastfed infant from Enstilar Foam or from the underlying maternal condition.

**Clinical Considerations**

To minimize potential exposure to the breastfed infant via breast milk, use Enstilar Foam on the smallest area of skin and for the shortest duration possible. Advise breastfeeding women not to apply Enstilar Foam directly to the nipple and areola to avoid direct infant exposure.

**Pediatric Use**

The safety and effectiveness of Enstilar Foam for the treatment of mild to severe plaque psoriasis have been established in pediatric patients 12 to 17 years. The use of Enstilar Foam for this indication is supported by evidence from adequate and well-controlled trials in adults and from one uncontrolled trial in 106 adolescents age 12 to 17 years with psoriasis of the body and scalp. Calcium metabolism was evaluated in all pediatric subjects and no cases of hypercalcemia or clinically relevant changes in urinary calcium were reported. Hypothalamic pituitary adrenal (HPA) axis suppression was evaluated in a subset of 33 pediatric subjects with moderate plaque psoriasis of the body and scalp (mean body surface area involvement of 16% and mean scalp area involvement of 56%). After 4 weeks of once daily treatment with a mean weekly dose of 47 grams, HPA axis suppression was observed in 3 of 33 subjects (9%). Because of a higher ratio of skin surface area to body mass, children under the age of 12 years are at particular risk of systemic adverse effects when they are treated with topical corticosteroids. Pediatric patients are, therefore, also at greater risk of HPA axis suppression and adrenal insufficiency with the use of topical corticosteroids including Enstilar Foam.

Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients treated with topical corticosteroids. Local adverse reactions including striae have been reported with use of topical corticosteroids in pediatric patients. The safety and effectiveness of Enstilar Foam in pediatric patients less than 12 years of age have not been established.

**Geriatric Use**

Of the total number of subjects in the controlled clinical studies of Enstilar Foam, 97 subjects were 65 years and over, and 21 were 75 and over. No overall differences in safety or effectiveness of Enstilar Foam were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

When calcipotriene was applied topically to mice for up to 24 months at dosages of up to 10 mg/kg/day (8, 30, and 90 mg/m²/day, respectively), no significant changes in tumor incidence were observed when compared to control. When betamethasone dipropionate was administered via oral gavage to male and female Sprague Dawley rats for up to 24 months at dosages of 20, 60, and 200 mg/kg/day (120, 360, and 1200 mg/m²/day, respectively), no significant changes in tumor incidence were observed when compared to control.

Calcipotriene did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, the human lymphocyte chromosome aberration test, or the mouse micronucleus test. Betamethasone dipropionate did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, or in the rat micronucleus test.

Studies in rats with oral doses of up to 54 mcg/kg/day (324 mcg/m²/day) of calcipotriene indicated no impairment of fertility or general reproductive performance. Studies in male rats at oral doses of up to 200 mcg/kg/day (1200 mcg/m²/day), and in female rats at oral doses of up to 1000 mcg/kg/day (6000 mcg/m²/day), of betamethasone dipropionate indicated no impairment of fertility.

**PATIENT COUNSELING INFORMATION**

**Flammability**

Advise patients that Enstilar Foams are flammable; avoid heat, flame, or smoking when applying this medication.

**Administration Instructions**

- Shake before use and spray the foam by holding the can in any orientation except horizontally.
- Do not use more than 60 grams every 4 days.
- Discontinue therapy when control is achieved until directed otherwise by the healthcare provider.
- Avoid use of Enstilar Foam on the face, underarms, groin or eyes. If this medicine gets on face or in mouth or eyes, wash area right away.
- Do not occlude the treatment area with a bandage or other covering unless directed by the healthcare provider. Instruct the patients not to use other products containing calcipotriene or a corticosteroid with Enstilar Foam without first talking to the healthcare provider.
- Wash hands after application.

**Local Reactions and Skin Atrophy**

Advise patients that local reactions and skin atrophy are more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids.

**Hypercalcemia and Hypercalciuria**

Advise patients that hypercalcemia and hypercalciuria have been observed with the use of Enstilar Foam.

**HPA Axis Suppression, Cushing's Syndrome, and Hyperglycemia**

Advise patients that Enstilar Foam can cause HPA axis suppression, Cushing's syndrome, and/or hyperglycemia.

**Ophthalmic Adverse Reactions**

Advise patients to avoid contact of Enstilar Foam with Eyes and to report any visual symptoms.

**Pregnancy and Lactation**

- Advise pregnant women that Enstilar® Foam may increase the potential risk of having a low birth weight infant and to use Enstilar Foam on the smallest area of skin and for the shortest duration possible.
- Advise breastfeeding women not to apply Enstilar Foam directly to the nipple and areola to avoid direct infant exposure.

**Manufactured by:** LEO Laboratories Ltd., 285 Cashel Road, Dublin 12, Ireland

**Distributed by:** LEO Pharma Inc., Madison, NJ 07940, USA

MAT-32588 March 2020
Lifestyle recommendations may curb symptoms

LIFESTYLE TAKES

Lifestyle recommendations are an interesting and complex aspect of eczema care. There are many things that can impact eczema severity and are found in a patient’s control to a certain extent. Finding suggestions to help patients can be challenging.

There are many things within a patient’s control that can impact eczema severity. It’s important that dermatologists help patients zero in on these, according to Peter A. Lio, M.D., clinical assistant professor of dermatology and pediatrics at Northwestern University Feinberg School of Medicine and founding partner, Medical Dermatology Associates of Chicago.

Lifestyle recommendations are an interesting and complex aspect of eczema care, says Dr. Lio, a speaker for the National Eczema Association. Age, for example, can greatly impact a patient’s willingness or ability to make lifestyle changes aimed at relieving symptoms of eczema. A challenge for many dermatologists is that so much of the eczema they see affects children under age two years. And for these patients, there are far fewer lifestyle options that could make an impact; yet, it’s generally much easier to change babies’ and toddlers’ lifestyles, Dr. Lio says.

Factors that can contribute significantly to eczema severity include sweating, exposure to chemicals or changing environments and stress, according to Dr. Lio. Determining which specific lifestyle factors—diet, exercise, environment—impact which patients is the hard part because it can vary from patient to patient, according to Dr. Lio.

“Stress often gets forgotten about, but there is very impressive evidence that it is part of the vicious cycle: stress worsens the skin and bad skin causes stress,” he says. And, diet, in Dr. Lio’s opinion, is almost always over-analyzed.

“I often say that I wish diet were the cause. It’s pretty easy to make changes there and could save an awful lot of suffering.”

Peter A. Lio, M.D., Northwestern University Feinberg School of Medicine, Chicago

“I just like to set realistic explanations. It is probably not the whole story. For some, the small improvements may not be worth the somewhat dramatic changes that may be required,” he says. Based on recommendations from providers and others, patients often try things like dustmite covers, air purifiers and water filters. Do they help?

“Maybe, sometimes. But my honest opinion is that, for the vast majority of patients, these are mostly expensive distractions that help us to regain a feeling that we have some control over the disease,” Dr. Lio says. “It’s just so hard because you want to be positive and supportive and help patients feel back in control, but you also want to focus on the things most likely to help and not overwhelm people with dozens of other things to do, especially when they are already likely stretched thin.”

Sound recommendations Dr. Lio often recommends atopic dermatitis patients get back to the basics, including with good education, good moisturization, gentle cleansing and good sleep habits. That’s where he starts.

“Appropriate use of topical steroids and incorporating non-steroidal medications when needed to keep inflammation down safely is the next step,” he says. “For those who are failing, getting another opinion, doing a skin biopsy, and/or patch testing to see if there is a component of allergic contact dermatitis are all important. Being prepared to think about phototherapy

or systemic treatments for those who are still not where they ought to be is the final step. Listening intently, being available for questions or concerns, and giving a written eczema action plan also are very helpful to my practice.”

Getting back to basics can help improve aspects of patients’ lives with far-reaching quality-of-life impact. Problems with sleep, for example, can be a vicious cycle for eczema patients. Dr. Lio says poor sleep damages the skin and inflamed skin disrupts sleep.

“It’s terrible,” he says. “I think that asking about sleep is one of the most important things. You can learn very quickly how well things are going if they are sleeping better. And often patients will ask for a sleeping pill, but I usually decline and remind them: ‘If this skin treatment works like I hope and expect it to, you won’t need help sleeping.’

Disclosure:
Dr. Lio has served as an investigator, speaker and advisor for Regeneron Genzyme, an investigator and advisor to AbbVie and Allergan; an investigator and speaker for L’Oreal, Pfizer, Pierre-Fabre, TopMD; and an advisor for Alba Labs, Amry, Dermacare, Dermati, Ellylu, Evolue, InteDerm, Johnson & Johnson, Kiniksa, La Trobe-Phaco, LEO Meric, Merosys, Reblin, Syncrea, Theraplex, Unilever and Venosa.
Quick TAKES

Reported prevalence of atopic dermatitis is higher in Europe than in the United States. Disease burden has been found to be higher in adolescents, which is a group that has not been well studied to date.

Burden of disease is high in adolescents

Over the years, studies have examined patient-reported disease burden either in clinical cohorts that may not be generalizable, or population-based cohorts in children or adults, says Jonathan Silverberg, M.D., Ph.D., MPH, director of clinical research, director of patch testing, and associate professor of dermatology at The George Washington University School of Medicine and Health Sciences, Washington, DC.

“A group that has not been studied well to date has been the adolescent population. There’s been a substantial amount of epidemiology work done in the adolescent age group from the ISAAC (International Study of Asthma and Allergies in Childhood) study, ages 13 to 14 years. Aside from that, we don’t have great data on burden of disease in older children and adolescents,” he says. “In addition, most studies of AD in childhood and adolescence used disparate methodology, which precludes the ability to compare results with studies of adult AD.”

The 1,377-patient Epidemiology of Children with Atopic Dermatitis Reporting on Their Experience (EPI-CARE) study is part of a large multinational study that examined AD across the entire life course. Between September 2018 and February 2019, investigators conducted a web-based survey of adolescents aged 12 to 17 years with AD in the United States, France, Germany, Italy, Spain and the UK. Average respondent age was 15 years, with a roughly even proportion of males and females at varying degrees of disease severity.

In one poster, Silverberg et al. reported a European AD prevalence of 14.7% versus 9.3% in the United States. European prevalence rates ranged from 8.7% in Germany to 19.8% in Spain. Regional differences regarding climate and genetics may account for the higher overall prevalence in Europe, Dr. Silverberg says.

“Part of it may also be related to the definition used in this study,” he adds. “To reduce the risk of potential misclassification, researchers combined self- or caregiver reporting of a doctor’s diagnosis of eczema or skin allergy with the extensively validated ISAAC criteria for AD.

“Adolescent dermatitis impacts all aspects of adolescent health,” Dr. Silverberg says. According to a separate poster, increasing disease severity correlated with increasing mean scores for itch, sleep, skin pain (all captured via a 0-10 numerical rating scale/NRS) and health-related quality-of-life (HRQOL).

The centrality of itch in AD has long been recognized, Dr. Silverberg says. “But we saw similar patterns for the intensity of sleep disturbances where patients with severe AD had NRS sleep of 7.1, which is considered to be severe sleep disturbance.”

EPI-CARE is one of the first studies to examine skin pain in the adolescent population, Dr. Silverberg adds. NRS scores for skin pain in patients with severe, moderate and mild AD were 7.5, 5.3 and 2.9, respectively (P<0.01 in all analyses).

“The real take-home comes down to the impact on quality of life. The more severe the atopic dermatitis, the more likely patients are to have substantial impact across all the different items and sub-domains of the Children’s Dermatology Life Quality Index (CDLQI),” Dr. Silverberg says. Similarly, the proportions of respondents in the severe, moderate and mild categories who reported having at least one atopic comorbidity were 81%, 68.6% and 64.3%, respectively.

“In addition, there is a substantial impact on productivity for adolescents,” he notes.

Average number of school days missed annually ranged from 10.9 (severe AD) to 3.4 (mild AD; P<0.01). Likewise, 87% of caregivers of an adolescent with severe AD reported missing at least one workday in the past four weeks, versus 66.3% for moderate AD and 44.8% for mild AD.

“When comparing the results from the study with previously published data in adults, ” write Prof. Stephen Weidinger and colleagues, “the disease burden associated with AD appears to be higher in adolescents than in adults, implying that there is an even greater unmet therapeutic need in the management of adolescents with moderate-to-severe AD.”

These results emphasize that the adolescent population would potentially benefit from tighter disease control, and potentially stepping up therapy, Dr. Silverberg says.

“The pediatric population has often been neglected from a therapeutic standpoint because pediatricians and pediatric dermatologists are often a little more hesitant about using some of the oral systemic immunosuppressants because of their toxicity and side-effect profile,” he says. “We are starting to see the development of newer, potentially more potent and safer therapeutics for the pediatric population. The growing recognition of the burden of AD in adolescents and hopefully better treatment options will allow for this patient population to be treated more appropriately and ultimately to achieve better long-term control of their disease.”

References:

Disclosures:
Dr. Silverberg has potential financial relationships with Galderma, Abbvie, Amgen, Allergan, Anacor, Amgen, Arena, Asana BioSciences, Arena, Boehringer Ingelheim, Dermira, Eli Lilly, Gilead, GlaxoSmithKline, GSK, Histolab, Inovio, LEO, LEO, Menlo, Novartis, Penguin, Pfizer, Regeneron, Shire, and Sotya.

B Y T H E N U M B E R S

Missed school days

Severe AD 10.9 DAYS
Mild AD 3.4 DAYS

Caregivers who report missing at least one workday

Moderate AD 33%
Severe AD 44%
Mild AD 23%

Caregivers of adolescents with severe AD were more likely to report missing at least one workday in the past four weeks.

“Quick TAKES”

We don’t have great data on burden of disease in older children and adolescents.”

Jonathan Silverberg, M.D., Ph.D., MPH, George Washington University School of Medicine and Health Sciences, Washington, DC
Study: Abrocitinib offers quick symptom relief

JOHN JESITUS | Staff Correspondent

A phase 2 study shows that the oral Janus kinase (JAK) 1 inhibitor abrocitinib (PF-04965842, Pfizer) quickly improved atopic dermatitis (AD) severity and symptoms versus placebo with some measures achieving statistically significant separation in days.

“We saw people having unbelievable clearance within weeks, which the data demonstrate. It was extremely surprising and very welcome for subjects on the trial,” says study co-author Seth B. Forman, M.D. He is owner of ForCare Medical Group in Tampa, Fla.

Investigators led by Melinda J. Gooderham, M.D., of SKiN Centre for Dermatology in Peterborough, Ontario, Canada, randomized 267 adults with moderate-to-severe AD to daily treatment with abrocitinib (200, 100, 30 or 10 mg) or placebo. In the 200-mg group, the proportion of patients who achieved Investigator Global Assessment (IGA) success from baseline peaked by weeks four to six and persisted through week 12. At 12 weeks, the proportions of patients in these groups were 82.6% and 59.0%, respectively, versus 35.2% for placebo.

Eczema Area and Severity Index (EASI) reductions showed significant improvement over placebo by week one in the 200 mg group and week two in the 100 mg group; these reductions were maintained for both groups. Week 12 EASI reductions for patients in these groups were 82.6% and 59.0%, respectively, versus 35.2% for placebo.

Regarding symptoms, pruritus scores showed significant improvement over placebo within two days of treatment in the 200 mg group (odds ratio 6.09; 90% confidence interval CI 1.35-27.59; p = 0.049). At week 12, least squares mean (LSM) differences versus placebo for the 200 mg and 100 mg doses were -25.4% (p = 0.003) and -20.7% (p = 0.02), respectively.

Among treatment-related adverse events, only gastrointestinal disorders were reported substantially more often for abrocitinib-treated patients than for those receiving placebo. The 200-mg dose, five patients (9.1%) experienced diarrhea, and eight patients (14.5%) experienced nausea. Gastrointestinal events did not appear to impact adherence or study withdrawal but will be monitored in future studies. Although platelet-count reductions peaked at week four in the 200-mg and 100-mg cohorts (29.8% and 11.4%, respectively), these levels trended toward normalization with continued treatment.

“For the JAK inhibitors as a class,” says Dr. Forman, “we need to monitor safety issues such as liver enzymes, platelets, neutrophils and tyrosine protein kinase (TPK). It’s a different mechanism of action than dupilumab.”

Seth B. Forman, M.D.
ForCare Medical Group, Tampa, Fla.

References:


Disclosures:

Dr. Forman is an investigator for AbbVie, AbbVie, Eli Lilly, Pfizer, Regeneron and XBiotech in the AD space.
Guidance on transitioning patients between biologics

CHERYL GUTTMAN KRADER, B.S. PHARM | Staff Correspondent

With many biologics now available for patients with moderate-to-severe plaque psoriasis, physicians may find themselves transitioning among them to optimize treatment and improve quality of life, according to Ron Vender, M.D., associate clinical professor of dermatology, McMaster University, and founder and director, Dermatrails Research, Inc., Hamilton, Ontario, Canada.

Switching among agents is one strategy to consider when patients fail to achieve an adequate response to biologic therapy, experience secondary failure with loss of efficacy over time, or develop an adverse reaction, he says. Dose or dosing interval adjustments may also be considered. In addition, there are also reports that repeating the induction phase regimen can help patients who are secondary failures.

What constitutes treatment failure is another issue to consider. The high PASI 90 response rates that can be achieved with the newer biologics have raised the bar. Individual patients, however, will differ in their outcome expectations, and use of adjuvant topical or phototherapy might be reasonable interventions to address localized resistant plaques in patients who fail to clear.

“Before making a switch for primary or secondary failure, clinicians also need to rule out a role for treatment nonadherence,” Dr. Vender says.

Dr. Vender recently published a paper that aims to provide clinicians with practical guidance for changing biologic therapy in patients being treated for moderate-to-severe plaque psoriasis who are deemed efficacy failures or develop a safety concern.1 He summarizes findings from relevant literature and offers recommendations about how and what biologic to transition to given different clinical scenarios.

Dr. Vender. He tells Dermatology Times that he undertook reviewing and synthesizing the literature on transitioning between biologics because of the absence of randomized, placebo-controlled trials comparing transitioning to different biologics and the paucity of guidance about when to start a new biologic for patients who were not responding to or not tolerating their existing biologic therapy.

“I believe my paper provides a guide as to when switching a biologic agent for treatment of moderate-to-severe plaque psoriasis is appropriate as well as information that will help clinicians make safe and effective choices when making the switch,” Dr. Vender says.

CHOOSE THE NEXT THERAPY

As with primary treatment decisions, patient comorbidities are factored into selecting the next biologic therapy. For patients with psoriatic arthritis, a TNF-α inhibitor or IL-17A blocker would be preferred because those agents have indications for both psoriasis and psoriatic arthritis.

For patients with inflammatory bowel disease, another relatively common comorbidity in patients with psoriasis, adalimumab (Humira, Abbvie), certolizumab (Cimzia, UCB), infliximab (Remicade, Janssen CarePath) and ustekinumab (Stelara, Janssen CarePath) are good choices since they are all approved for treatment of Crohn disease and/or ulcerative colitis, but IL-17 blockers should be avoided.

In patients with manual dexterity issues, consideration can be given to a biologic that can be administered with an auto-injector. Otherwise, reports in the literature indicate that in cases of insufficient response, switching to another biologic within the same class or to a biologic in a different class can both be safe and effective strategies.

TIMING THE TRANSITION

Recommendations regarding the timing for starting a different biologic differ based on whether the switch is being made due to safety concerns or lack of efficacy. If a change is being made because the patient experienced an adverse event with existing biologic treatment, evidence supports waiting until the reaction has resolved or elevated laboratory parameters have normalized or stabilized.

In the situation where the reason for switching is lack of efficacy, Dr. Vender suggests beginning the new biologic when the existing therapy was last scheduled for administration or based on the minimal or shortest dosing interval for the failed agent’s induction schedule.

For example, in the case where a patient is failing treatment with etanercept (Enbrel, Amgen), a new biologic could be started one week after the last etanercept dose. The switch to a new biologic can be made two weeks after the last dose of adalimumab, infliximab, certolizumab, secukinumab (Cosentyx, Novartis), ustekinumab (Taltz, Eli Lilly) or brodalumab (Siliq, Valeant Pharmaceuticals), while a four-week delay before switching is suggested when treatment is being transitioned from ustekinumab, guselkumab (Tremfya, Janssen CarePath), tildrakizumab (Ilumya, Sun Pharma), or risankizumab (Skyrizi, Abbvie).

Available evidence seems to weigh against the need to wait for washout of the existing therapy, according Dr. Vender.

“The washout period for biologics is usually considered to be four half-lives,” he says. “Waiting that long to begin a new biologic can put patients at risk for worsening of their disease and quality of life, and the likelihood for that occurring appears to be greater than the likelihood that overlapping therapies will result in an adverse effect,” he explains. 

Disclosure: Dr. Vender has received grants and research support from companies that market biologics for treatment of plaque psoriasis. He received no financial support for the research, authorship, or publication of this article on transitioning between biologics.

IL-23 inhibitors may offer longer-lasting results

JOHN JESITUS | Staff Correspondent

With extended remissions, high safety and favorable dosing schedules, interleukin (IL)-23 inhibitors are well-suited for a variety of patients with psoriasis, says an expert who spoke at the South Beach Symposium.

The IL-23 inhibitors’ mechanism of action and infrequent dosing schedule provide advantages over previous-generation biologics, says Mark Lebwohl, M.D. He is the Waldman Professor and Chairman, Kimberly and Eric J. Waldman Department of Dermatology, Icahn School of Medicine at Mount Sinai.

“In the pathophysiology of psoriasis, the key target appears to be IL-17,” he says. The IL-23 blockers guselkumab (Tremfya, Janssen CarePath), tildrakizumab (Ilumya, Sun Pharma), risankizumab (Skyrizi, AbbVie) and mirikizumab (LY3074828, Eli Lilly) block the cytokine that upregulates the Th17 cell, which makes IL-17. The Th17 cell not only stops making IL-17, but then either hibernates or withers away, according to Dr. Lebwohl.

Then it takes several months to reconstitute those cells. So these drugs work more slowly than the IL-17 inhibitors, but their effect is longer lasting,” he adds.

Brodalumab (Siliq, Valeant Pharmaceuticals), ixekizumab (Tolzta, Eli Lilly) and secukinumab (Cosentyx, Novartis) can provide 50% Psoriasis Area and Severity Index (PASI) reductions in 1.8 to 3 weeks, but with IL-23 inhibitors, “patients really only start getting gone after four weeks,” says Dr. Lebwohl.

But the IL-23 blockers are highly efficacious, he notes, and results typically peak around week 22. Once patients reach maximum efficacy, they typically maintain response for years. For example, guselkumab phase 3 data examining patients with moderate disease showed that with injections every two months, 71.8% and 77.2% of patients achieved PASI 90 at weeks 16 and 24, respectively, versus 48.2% and 54.1% for adalimumab (p < 0.001).

“IL-23 blockers’ efficacy, dosing schedules and extended remissions make them ideal for patients on Medicare Part D. After these patients reach the “doughnut hole,” they must pay the amount of the doughnut hole plus 5% of their drug costs above the doughnut hole.

“That comes to about $9,000 a year for some drugs,” says Dr. Lebwohl. “Many patients can’t afford that.”

Because IL-23 blockers are administered in hospitals, however, they count toward patients’ medical benefits. “So it doesn’t cost the patient anything,” he notes. “That’s a real plus.”

Additional patients for whom these drugs are proving especially useful include those who travel frequently, or cannot get to the hospital regularly, such as prisoners or those in other institutions.

“They can get injections as infrequently as every three months. And then there are patients who are difficult to inject, such as those with Parkinson’s disease. This is ideal — they only come in four times a year to get the injection.”

The high efficacy of IL-23 inhibitors means that unlike with most biologic drugs, obese patients lose very little response. The category shows promise for psoriatic arthritis, Dr. Lebwohl adds, although IL-17 inhibitors presently dominate this indication.

Reference:
Mark Lebwohl MD “Tips in the Use of Anti-IL-23 Antibodies,” South Beach Symposium February 9, 2020

Disclosures:
Dr. Lebwohl has been an investigator and advisor for guselkumab (Janssen), tildrakizumab (Sun Pharma), risankizumab (AbbVie) and mirikizumab (Eli Lilly) and most of the biologic therapies available for psoriasis. All payments for research go to his employer, the Icahn School of Medicine at Mount Sinai, and he receives no personal direct compensation from the manufacturers of biologic therapies.
**INDICATION**

SILIQ® injection is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.

**IMPORTANT SAFETY INFORMATION**

**WARNING: SUICIDAL IDEATION AND BEHAVIOR**

Suicidal ideation and behavior, including completed suicides, have occurred in patients treated with SILIQ. Prior to prescribing SILIQ, weigh the potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior. Patients with new or worsening suicidal ideation and behavior should be referred to a mental health professional, as appropriate. Advise patients and caregivers to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes [see Warnings and Precautions (5.1) in the full Prescribing Information].

Because of the observed suicidal behavior in subjects treated with SILIQ, SILIQ is available only through a restricted program called the SILIQ REMS Program [see Warnings and Precautions (5.2) in the full Prescribing Information].

**Crohn’s Disease** SILIQ is contraindicated in patients with Crohn’s disease. In clinical trials, which excluded Crohn’s patients, one SILIQ patient was withdrawn after developing Crohn’s disease.

**SILIQ Risk Evaluation and Mitigation Strategy (REMS) Program** SILIQ is available only through a restricted program called the SILIQ REMS Program because of observed suicidal ideation and behavior in patients treated with SILIQ. Before prescribing SILIQ, prescribers must be certified with the program, have each patient sign a Patient-Prescriber Agreement Form, and provide the patient a Wallet Card describing symptoms requiring immediate medical evaluation. Pharmacies must be certified and only dispense to patients authorized to receive SILIQ. More information is available at SILIQREMS.com.

**Infections** SILIQ may increase the risk of infections. Serious infections and fungal infections were observed at a higher rate in patients treated with SILIQ than placebo-treated patients in clinical trials, including one case of cryptococcal meningitis that led to discontinuation of therapy.

- Consider risks and benefits prior to prescribing SILIQ in patients with a chronic infection or history of recurrent infection
- Instruct patients to seek treatment if signs or symptoms of a chronic or acute infection occur

Please see additional Important Safety Information and Brief Summary of Full Prescribing Information on the following pages.
If at first they don’t succeed, you could try, try again.  
Or you could just try SILIQ.

You know the unique challenges that come with treating moderate to severe plaque psoriasis. There is no cure. No guarantees of lasting success. No shortage of setbacks. Your patients need a reason to believe, and SILIQ can renew that hope, even if they’ve failed on other treatments.\(^1\)\(^3\)

In a clinical study, 42% of SILIQ patients achieved 100% clear skin at 12 weeks (vs 0.5% of placebo patients), and 68% were totally clear at 52 weeks (vs 0 placebo patients).\(^4\) And many patients who failed other systemic and biologic treatments have found significant results with SILIQ.\(^1\)\(^3\)

**SILIQ rescue* after anti-IL-17A failures**
in an open-label trial (N=39)\(^2\)

- **Response rate in patients who had success with SILIQ at 16 weeks after failure with anti-IL-17A agents.**  
  - Failure defined as not achieving a PASI75 after 3 months of treatment or a loss of 50% or more of the original improvement.

\(44.0\%\) **PASI 90**  
\(28.0\%\) **PASI 100**

**SILIQ rescue* after anti-IL-12/23 failure**
in two phase 3 trials (N=124)\(^3\)

- **Response rate in patients who had success with SILIQ at 52 weeks after failure with an anti-IL-12/23 agent at 16 weeks.** Failure defined as a single sPGA score of ≥3 or persistent sPGA scores of ≥2 for at least a 4-week period.

\(58.1\%\) **PASI 90**  
\(36.3\%\) **PASI 100**

**SILIQ rescue* after anti-TNF-α failures**
in two phase 3 trials (N=150)\(^4\)

- **Response rate in patients who had success with SILIQ at 12 weeks after failure with anti-TNF-α agents.**  
  - Failure defined as non-response to treatment (primary inefficacy), a secondary loss of efficacy over time or, development of an intolerance to the biological agent [drug reaction or adverse event].

\(62.7\%\) **PASI 90**  
\(32.0\%\) **PASI 100**

*Rescue is defined as treatment with SILIQ after failure with another/other treatment(s) and is the term used in the SILIQ clinical studies.

---

**IMPORTANT SAFETY INFORMATION (cont’d)**

**Risk for Latent Tuberculosis (TB) Reactivation** Evaluate patients for TB prior to initiating treatment with SILIQ and do not treat patients with active TB. Initiate treatment for latent TB prior to starting SILIQ and consider anti-TB therapy prior to initiation in patients with history of latent TB if adequate treatment cannot be confirmed. Monitor closely for symptoms of active TB during and after treatment.

**Immunizations** Avoid use of live vaccines in patients treated with SILIQ.

**Adverse Reactions** The most commonly reported adverse reactions in clinical trials were arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, myalgia, injection site reactions, influenza, neutropenia, and tinea infections.

To report SUSPECTED ADVERSE REACTIONS, contact Customer Service at 1-800-321-4576 or FDA at 1-800-FDA-1088, or visit www.fda.gov/MedWatch.

Please see Brief Summary of Full Prescribing Information on the following page, including Boxed Warning about suicidal ideation and behavior.

**References:**
Infections:
- Prescribers must be certified with the program.
- SILIQ REMS Program:
  - SILIQ is available only through a restricted program under a REMS

Suicidal Ideation and Behavior:
- SILIQ use may increase the risk of suicidal ideation and behavior in clinical trials. There was a higher proportion of cases of suicidal ideation and behavior as compared to users without such a history.

**Warnings and Precautions**

Suiclidal Ideation and Behavior: Suicide ideation and behavior, including 4–controlled suicidies, occurred in subjects treated with SILIQ in the psoriasis clinical trials. There were no completed suicides in the 12-week placebo-controlled portion of the trials. SILIQ users have a history of suicide or depression or an increased incidence of suicidal ideation and behavior as compared to users without such a history. A causal association between treatment with SILIQ and increased risk of suicide and behavior is not established. Prescribers should weigh the potential risks and benefits before using SILIQ in patients with a history of depression or suicidality. Patients with new or worsening symptoms of depression or suicidality should be referred to a mental health professional, as appropriate, and prescribers and caregivers should be made aware of the potential for suicidal risk to be a concern in patients treated with SILIQ and those treated with ustekinumab. Through the end of the trial, the exposure-adjusted rates of treatment-emergent suicidal ideation or behavior were similar to those seen in the 12-week period in the subjects treated with SILIQ.

**Specific Adverse Reactions:**
- Suicidal ideation and behavior: During the 12-week randomized treatment period in the pooled trials, one subject in the SILIQ group attempted suicide and none in the placebo or ustekinumab groups. From initiation through Week 52 of the trials, suicidal ideation or behavior occurred in 8 of 769 subjects (0.9 per 100 subject-years) treated with SILIQ and 2 of 613 subjects (0.4 per 100 subject-years) treated with ustekinumab.

- During the course of the clinical trials for plaque psoriasis, suicidal ideation or behavior occurred in 34 of 4446 subjects treated with SILIQ (0.7 per 100 subject-years). Eight of the 10 subjects who attempted or completed suicide had a history of depression and/or suicidal ideation or behavior.

**Drug Interactions**

Live Vaccinations: Avoid use of live vaccines in patients treated with SILIQ. [see Warnings and Precautions]

**CYP450 Substrates:** The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-12, IL-23), IL-15, and TNF during chronic, active disease. Therefore, monitor patients receiving concomitant drugs which are CYP450 substrates when SILIQ is initiated or discontinued. Consider replacing the CYP450 substrate with an alternative drug, if possible.

**USP CODES:**

Pregnancy: There are no human data on SILIQ use in pregnant women to inform a drug-associated risk. Human IgG antibodies are known to cross the placental barrier, therefore SILIQ may be transmitted from the mother to the breastfed infant. The effects of SILIQ on the breastfed infant, or the effects on milk production. Brodalumab was detected in the milk of lactating cynomolgus monkeys. The human IgG antibodies are known to cross the placental barrier; therefore, SILIQ may be transmitted from the mother to the breastfed infant.

**Lactation:** There are no data on the presence of brodalumab in human milk, the effects on the breastfed infant, or the effects on milk production. Brodalumab was detected in the milk of lactating cynomolgus monkeys. The effects of SILIQ on the breastfed infant, or the effects on milk production. Brodalumab was detected in the milk of lactating cynomolgus monkeys. The effects of SILIQ on the breastfed infant, or the effects on milk production. Brodalumab was detected in the milk of lactating cynomolgus monkeys.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Animal studies have not been conducted to evaluate the carcinogenic potential of SILIQ. 

**Nonclinical Toxicology**

- Nonclinical studies have not been conducted to evaluate the carcinogenic potential of SILIQ. 

**Human Milk:** Human IgG antibodies are known to cross the placental barrier; therefore, SILIQ may be transmitted from the mother to the breastfed infant. The effects of SILIQ on the breastfed infant, or the effects on milk production. Brodalumab was detected in the milk of lactating cynomolgus monkeys.

CT0430_039_AD OrthoDerm Silique.indd 25
CT0430_039_AD OrthoDerm Silique.indd 25
3/26/20 8:32 AM
Until recently, few effective treatment options were available for the treatment of advanced basal cell carcinoma (aBCC), with different chemotherapeutic agents finding only marginal success in some case reports. However, continued research has produced a number of targeted therapies that provide hope for patients with this rare but sometimes deadly form of nonmelanoma skin cancer.

“Before the emergence of molecular targeted therapies, patients with metastatic or advanced basal cell carcinoma were very challenging to treat, with truly effective treatments few and far between. The dawn of the hedgehog inhibitors has changed the way we treat our advanced basal cell carcinoma patients,” says Desiree Ratner, M.D., clinical professor, Ronald O. Perelman department of dermatology, NYU Skin and Cancer Clinic, New York, who recently spoke at the Orlando Dermatology Aesthetic and Clinical conference in Orlando.

Following the FDA approval of the two hedgehog inhibitors vismodegib (Erivedge, Genentech) and sonidegib (Odomzo, Sun Pharma) in 2012 and 2015, respectively, clinicians could finally offer a novel oral therapy to their patients with advanced basal cell carcinoma.

While vismodegib is approved for locally advanced and metastatic basal cell carcinoma, sonidegib is only approved for locally advanced basal cell carcinoma. Both agents are small molecular inhibitors of smoothened homolog (SMO), which block hedgehog signaling activation. After only having chemotherapy or high dose radiation therapy as medical treatment options, Dr. Ratner says that the oral hedgehog inhibitors are a welcome addition to the clinician’s armamentarium for advanced BCC.

“These targeted therapeutic drugs basically give us a viable treatment alternative for large basal cell tumors that are unresectable or not amenable to radiation therapy,” Dr. Ratner says. Though having a proven efficacy in patients with advanced basal cell carcinoma, the hedgehog inhibitors also have significant side effects, the most common of which are muscle spasms, hair loss, and dysgeusia, but can also include nausea, vomiting, diarrhea, constipation and fatigue, all of which can sometimes be difficult for patients to tolerate. As a result, Dr. Ratner says that clinicians are now suggesting that patients on hedgehog inhibitor therapy take a drug holiday from their treatment protocol to offer relief from the potential side effects while maintaining treatment goals. According to Dr. Ratner, those patients who have intolerable adverse reactions can have up to an 8-week dose interruption drug holiday, and then can start the drug again, without interrupting the long-term therapeutic benefit of the medication.

Those metastatic or advanced basal cell carcinoma patients who had unresectable disease or were not candidates for radiation therapy historically were treated with various regimens of conventional cytotoxic chemotherapies that achieved less than satisfactory therapeutic outcomes. For most cases, Dr. Ratner says that the hedgehog inhibitors have practically made chemotherapy obsolete for the treatment of advanced basal cell carcinoma.

“We now have treatments for patients with advanced basal cell carcinoma that we could not have imagined 10 years ago that are providing patients with effective and durable remissions of their disease. We don’t know yet whether they are going to be effective in the long term but at least in the short term, they are giving patients a quality of life and a disease-free interval that is longer than they could have previously achieved,” Dr. Ratner says.

**Disclosures:**
Dr. Ratner reports no relevant disclosures.
Cosmetic Surgery Forum

THE JW MARRIOTT • NASHVILLE, TN

December 2-5, 2020

REGISTER TODAY, SAVE $150

Attendees can save $150 on CORE tickets**

CosmeticSurgeryForum.com

Course Director: Joel Schlessinger, MD

-HONEST-
“What I like about this particular meeting is that it’s so intimate and it’s so interactive. You have the opportunity to ask questions of the panelist and have this whole interaction about their experience. I really like that because it’s about sharing what everybody is actually doing in their practices, not just evidence-based but anecdotal and experiential.”

- CHYTRA ANAND, MD

-PRACTICAL-
“What I love about this meeting every year is that it incorporates everyone in the audience into every single session so you get so many points of view. The talks are fast-paced and to the point so you get solid bullet-point information that you can directly use in your practice. Every year, I’m more impressed with the amount of data that I have to take home and have an impact for my practice and for my patients. It’s a whirlwind of a meeting—action-packed, busy, fun and informative. I love it every year.”

- DORIS DAY, MD

-INSIGHTFUL-
“I think one of the best aspects of Cosmetic Surgery Forum is everyone talks about their experience, especially experiences in their practice that are not necessarily on-label, but off-label. I learn so much about what other people are doing that I can apply to my own practice that’s safe, great for patients and that everyone can benefit from.”

- LAWRENCE GREEN, MD

*CME credits are subject to change. This activity has been approved for up to 19 AMA PRA Category 1 Credits™. **Offer ends June 16, 2020.

For more information, please contact: Natasha Mohr or Meg Housholder • info@CosmeticSurgeryForum.com • 402-697-6564
A paradigm shift in cSCC treatment

ILYA PETROU, M.D. | Staff Correspondent

Recent advances in systemic therapies have led to the development of PD-1 checkpoint inhibitors, which one expert says may represent a paradigm shift in the treatment and management of patients with locally advanced or metastatic cutaneous squamous cell carcinoma (cSCC), and particularly for metastatic SCC tumors that may not be amenable to surgical resection or radiation therapy.

“The increasing numbers of SCC that are found in our population especially in fair skinned and older patients are typically addressed with some form of surgery and/or other treatment modalities. When these tumors become more advanced however, that’s when you have to think about other treatments such as the check point inhibitors, among other therapies,” says Todd E. Schlesinger, M.D., FAAD, medical director, Dermatology & Laser Center and Clinical Research Center of the Carolinas, Charleston, S.C., who recently delivered a CME presentation during the Maui Derm for Dermatologists meeting, Maui, Hawaii.

Recently, the FDA approved cemiplimab (Libtayo, Regeneron and Sanofy Genzyme) for the treatment of cutaneous locally advanced and metastatic SCC. In the combined phase 1/2 clinical trial data, the monoclonal antibody achieved an overall response rate of approximately 50% of patients as well as a durable response exceeding six months in 57% of responders.

According to Dr. Schlesinger, the response with cemiplimab is a remarkable improvement from the outcomes achieved with previously used approaches with higher toxicities, which historically have demonstrated only a 15% to 35% overall patient response rate.

Advanced SCC is thought to be particularly responsive to immunotherapy because the disease risk is strongly associated with immunosuppression and it has a very high tumor mutational burden, which is five times that of lung cancer and over four times that of melanoma.

The complex interplay between SCC tumors and the immune system leads to their pathogenesis and, in response, the body develops ways to initiate immune surveillance to try to keep these mutations and the tumors under control. According to Dr. Schlesinger, immune surveillance plays a key role in addressing the tumors and keeping them at bay.

“That is the whole point of checkpoint inhibition, where the PD-1 inhibitors block that interaction between the T-cell and tumor cell. This basically ‘uncloaks’ the tumor cells and creates a reaction that causes the tumor cells to be destroyed via the CD8+ T-cell pathway.”

That is the whole point of checkpoint inhibition, where the PD-1 inhibitors block that interaction between the T-cell and tumor cell. This basically ‘uncloaks’ the tumor cells and creates a reaction that causes the tumor cells to be destroyed via the CD8+ T-cell pathway.”

Dr. Schlesinger says.

Certainly, the checkpoint inhibitors are fraught with adverse events (AE) that are primarily related to immune system activation that can affect any organ system. However, Dr. Schlesinger says there is a general sense among clinicians and their patients that AEs — even those that are severe — are low compared with those from other therapies. Most of the AEs do not require treatment interruption and can be managed by the treating physician. As such, the potential benefit that patients can receive from this medication oftentimes outweighs the adverse events that the patients may have.

Past and current trials with PD-1 inhibitors for the treatment of advanced SCC were conducted in generally healthy individuals and, as such, Dr. Schlesinger says that caution is warranted when considering PD-1 therapy in OTRs and otherwise immunosuppressed patients or those with significant comorbidities.

At present, adjuvant radiation therapy may be considered for advanced SCC if surgical therapy is not feasible or preferred. However, the precise role of radiation therapy is still to be elucidated, especially when using it in combination with checkpoint inhibition. According to Dr. Schlesinger, salvage radiation therapy (SRT) seems to be falling out of favor recently for some cases as recent data indicates that its implementation may lead to a worse prognosis.

“The immune checkpoint inhibitors are a new paradigm for the treatment of advanced SCC. Ongoing clinical trials will help elucidate the therapeutic benefit of cemiplimab as well as other PD-1 agents currently under investigation,” Dr. Schlesinger says.

Disclosures:
Dr. Schlesinger is a consultant and clinical investigator for both Regeneron and Sanofi, and he is the spokesperson for the Regeneron/Sanofi alliance.
GETTING OTEZLA GETS EVEN EASIER

8 out of 10 commercially insured lives in the US have preferred access with no biologic step required for Otezla.¹

Otezla is listed as preferred, with no biologic step requirement, on:

- Aetna Prescription Drug Benefit
- Cigna Prescription Drug List
- CVS Caremark Formularies*
- Express Scripts National Preferred Formulary†
- OptumRx
- Prime Therapeutics
- UnitedHealthcare

Indicates no DMARD or biologic step-edit required.

Contact your Otezla representative or visit otezlapro.com for a complete list of plans

*Basic, Standard, and Advanced Control Formularies.
†SafeGuardRx® Program has 1 biologic step for patients on certain Otezla indications.
DMARD, disease-modifying antirheumatic drug.

Please see accompanying Brief Summary of Full Prescribing Information.


Otezla® is a registered trademark of Celgene Corporation. © 2019 Celgene Corporation 04/19 US-OTZ-19-0305
INDICATIONS

- Otezla® (apremilast) is indicated for the treatment of adult patients with active psoriatic arthritis
- Otezla is indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy

Otezla: the ONLY ORAL treatment indicated for psoriatic arthritis and plaque psoriasis

IMPORTANT SAFETY INFORMATION

Contraindications
- Otezla® (apremilast) is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation

Warnings and Precautions
- Diarrhea, Nausea and Vomiting: Cases of severe diarrhea, nausea, and vomiting were associated with the use of Otezla. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting; advise patients to contact their healthcare provider. Consider Otezla dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting
- Depression: Carefully weigh the risks and benefits of treatment with Otezla for patients with a history of depression and/or suicidal thoughts/behavior, or in patients who develop such symptoms while on Otezla. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and they should contact their healthcare provider if such changes occur
  - Psoriasis: Treatment with Otezla is associated with an increase in depression. During clinical trials, 1.3% (12/920) of patients reported depression compared to 0.4% (2/506) on placebo; Depression was reported as serious in 0.1% (1/1308) of patients exposed to Otezla, compared to none in placebo-treated patients (0/506). Suicidal behavior was observed in 0.1% (1/1308) of patients on Otezla, compared to 0.2% (1/506) on placebo. One patient treated with Otezla attempted suicide; one patient on placebo committed suicide
  - Psoriatic Arthritis: Treatment with Otezla is associated with an increase in depression. During clinical trials, 1.0% (10/998) reported depression or depressed mood compared to 0.8% (4/405) treated with placebo. Suicidal ideation and behavior was observed in 0.2% (3/1441) of patients on Otezla, compared to none in placebo treated patients. Depression was reported as serious in 0.2% (3/1441) of patients exposed to Otezla, compared to none in placebo treated patients (0/495). Two patients who received placebo committed suicide compared to none on Otezla
- Weight Decrease: Monitor body weight regularly; evaluate unexplained or clinically significant weight loss, and consider discontinuation of Otezla
  - Psoriasis: Body weight loss of 5-10% occurred in 12% (96/784) of patients treated with Otezla and in 5% (19/382) of patients treated with placebo. Body weight loss of ≥10% occurred in 2% (16/784) of patients treated with Otezla compared to 1% (3/382) of patients treated with placebo
  - Psoriatic Arthritis: Body weight loss of 5-10% was reported in 10% of patients taking Otezla and in 3.3% of patients taking placebo
- Drug Interactions: Apremilast exposure was decreased when Otezla was co-administered with rifampin, a strong CYP450 enzyme inducer; loss of Otezla efficacy may occur. Concomitant use of Otezla with CYP450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended

With a proven efficacy and safety profile, oral dosing, and no label-required lab monitoring, Otezla is a treatment experience patients can respond to.*

RESULTS

the way

THEY WANT THEM

© 2019 Celgene Corporation

Otezla® is a registered trademark of Celgene Corporation.

Data on file, Celgene

Plain Text
PSORIATIC ARTHRITIS

Significant joint improvement\(^{1,3}\)

In PALACE\(^{1}\)TM 1

38% ACR20 response with Otezla\(^{®}\) (apremilast) 30 mg twice daily (n = 168) vs 19% with placebo (n = 168) at week 16 (primary endpoint; \(P = 0.0001\))

\(^{1}\)The efficacy and safety of Otezla in psoriatic arthritis was evaluated in 3 multicenter, randomized, double-blind, placebo-controlled phase 3 trials in adult patients with active psoriatic arthritis (N = 1493). Patients were randomized 1:1:1 to either Otezla 30 mg twice daily, Otezla 20 mg twice daily, or placebo for 24 weeks, after a 5-day titration period. In PALACE 1, Otezla significantly increased ACR20 response (n = 168) at week 16 (primary endpoint) vs placebo (n = 168) (38% vs 19%; \(P = 0.0001\)).

Safety profile: The most common adverse reactions (≥5%) were diarrhea, nausea, and headache.\(^1\)

PALACE 1-3 clinical development program\(^{1,2}\)

- Otezla was studied in 3 randomized, double-blind, placebo-controlled trials of similar design
- Adult patients (N = 1493) with psoriatic arthritis for at least 6 months, now with active psoriatic arthritis (≥3 swollen joints and ≥3 tender joints) despite prior or current DMARD therapy, were randomized 1:1:1 to placebo, Otezla 20 mg, or Otezla 30 mg given twice daily, after an initial 5-day titration
- Patients who were therapeutic failures of ≥3 agents for psoriatic arthritis (small molecules or biologics) or >1 biologic TNF-a inhibitor were excluded
- Placebo-controlled efficacy data were collected and analyzed through week 24. Placebo nonresponders at week 16 were re-randomized to either 20 mg twice daily or 30 mg twice daily Otezla. At week 24, all remaining patients receiving placebo were re-randomized to either 20 mg twice daily or 30 mg twice daily. Patients treated with Otezla remained on their initial treatment. Patients entering a long-term extension phase could be treated through 5 years
- 65% of patients received concomitant therapy with at least one DMARD, including 55% methotrexate

MODERATE TO SEVERE PLAQUE PSORIASIS

Significant skin improvement\(^{1,4}\)

In ESTEEM\(^{®}\) 1

33% PASI-75 response with Otezla 30 mg twice daily (n = 562) vs 5% with placebo (n = 282) at week 16 (primary endpoint; \(P < 0.0001\))

\(^{1}\)The efficacy and safety of Otezla in plaque psoriasis was evaluated in 2 multicenter, double-blind, placebo-controlled trials of similar design. Patients with moderate to severe plaque psoriasis (N = 1257) were randomized 2:1 to Otezla 30 mg twice daily or placebo for 16 weeks after a 5-day titration.\(^{1,4}\) In ESTEEM 1, Otezla significantly increased PASI-75 response (n = 562) at week 16 (primary endpoint) vs placebo (n = 282) (33% vs 5%; \(P < 0.0001\)).

Safety profile: The most common adverse reactions (≥5%) were diarrhea, nausea, upper respiratory tract infection, tension headache, and headache.\(^{1}\)

ESTEEM clinical development program

- Evaluated in a multicenter, double-blind, placebo-controlled trial. Patients with moderate to severe plaque psoriasis (N = 844) were randomized 2:1 to Otezla 30 mg twice daily or placebo for 16 weeks after a 5-day titration\(^{1}\)
- At week 16, all patients originally assigned to placebo transitioned to Otezla 30 mg twice daily. At week 32, some patients originally randomized to Otezla were based on clinical response, re-randomized to Otezla or placebo. Those re-randomized to placebo restarted Otezla 30 mg twice daily at loss of response, but no later than week 52\(^{1,4}\)
- Selected inclusion criteria: Age ≥18 years, BSA involvement ≥10%, sPGA ≥3, PASI score ≥12, candidates for phototherapy or systemic therapy\(^1\)
- Patients entering a long-term extension phase could be treated through 5 years\(^4\)

ACR, American College of Rheumatology; BSA, body surface area; DMARD, disease-modifying antirheumatic drug; ESTEEM, Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; PALACE, Psoriatic Arthritis Long-Term Assessment of Clinical Efficacy; PASI, Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment; TNF, tumor necrosis factor.

Adverse Reactions

- Psoriasis: Adverse reactions reported in ≥5% of patients were (Otezla%, placebo%): diarrhea (17, 6), nausea (17, 7), upper respiratory tract infection (9, 6), tension headache (8, 4), and headache (6, 4)
- Psoriatic Arthritis: Adverse reactions reported in at least 2% of patients taking Otezla, that occurred at a frequency at least 1% higher than that observed in patients taking placebo, for up to 16 weeks (after the initial 5-day titration), were (Otezla%, placebo%): diarrhea (7, 1.6); nausea (8.9, 3.1); headache (5.9, 2.2); upper respiratory tract infection (3.9, 1.8); vomiting (3.2, 0.4); nasopharyngitis (2.6, 1.6); upper abdominal pain (2.0, 0.2)

Use in Specific Populations

- Pregnancy and Nursing Mothers: Otezla is Pregnancy Category C; it has not been studied in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether apremilast or its metabolites are present in human milk. Caution should be exercised when Otezla is administered to a nursing woman
- Renal Impairment: Otezla dosage should be reduced in patients with severe renal impairment (creatinine clearance less than 30 mL/min); for details, see Dosage and Administration, Section 2, in the Full Prescribing Information

Please turn the page for Brief Summary of Full Prescribing Information.


Otezla\(^{®}\) is a registered trademark of Celgene Corporation. © 2019 Celgene Corporation 07/19 US-OTZ-19-0653
OTEZLA® (apremilast) tablets, for oral use

The following is a Brief Summary of the Prescribing Information; see Full Prescribing Information for complete product information.

CONTRAINDICATIONS
OTEZLA is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation [see Adverse Reactions (6.1)].

WARNINGS AND PRECAUTIONS
Diarhea, Nausea, and Vomiting: There have been postmarketing reports of severe diarrhea, nausea, and vomiting in patients with psoriasis who were started on OTEZLA within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting. Patients who reduced dosage or discontinued OTEZLA generally improved quickly. Consider OTEZLA dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting.

Depression: Treatment with OTEZLA is associated with an increase in adverse reactions of depression. Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of OTEZLA for children and young adults.

Psoriatic arthritis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.0% (10/986) of subjects treated with OTEZLA reported depression or depressed mood compared to 0.8% (4/445) treated with placebo. During the clinical trials, 0.3% (4/1441) of subjects treated with OTEZLA discontinued treatment due to depression or depressed mood compared to none in placebo treated subjects (0/495). Depression was reported as serious in 0.2% (2/1441) of subjects exposed to OTEZLA, compared to none in placebo treated subjects (0/495). Incidences of suicidal ideation and suicidal behavior have been observed in 0.2% (3/1441) of subjects after receiving OTEZLA, compared to none in placebo treated subjects (0/495). In the clinical trials, 2 subjects who received placebo committed suicide compared to none in OTEZLA treated subjects.

Psoriasis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.3% (35/2510) of subjects treated with OTEZLA reported depression compared to 0.4% (25/556) treated with placebo. During the clinical trials, 0.1% (1/1308) of subjects treated with OTEZLA discontinued treatment due to depression compared with none in placebo treated subjects (0/506). Depression was reported as serious in 0.1% (1/1308) of subjects exposed to OTEZLA, compared to none in placebo treated subjects (0/506). Instances of suicidal ideation and suicidal behavior have been observed in 0.1% (1/1308) of subjects while receiving OTEZLA, compared to 0.2% (2/1586) in placebo-treated subjects. In the clinical trials, one subject treated with OTEZLA attempted suicide while one who received placebo committed suicide.

Weight Decrease: During the controlled period of the studies in psoriatic arthritis (PsA), weight decrease between 5%-10% of body weight was reported in 10% (48/471) of subjects treated with OTEZLA 30 mg twice daily compared to 3.3% (16/495) treated with placebo [see Adverse Reactions (6.1)].

During the controlled period of the trials in psoriasis, weight decrease between 5%-10% of body weight occurred in 12% (65/564) of subjects treated with OTEZLA compared to 5% (19/382) treated with placebo. Weight decrease of 10% or more of body weight occurred in 2% (16/784) of subjects treated with OTEZLA 30 mg twice daily compared to 1% (3/382) subjects treated with placebo.

Patients treated with OTEZLA should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of OTEZLA should be considered.

Drug Interactions: Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of OTEZLA. Therefore, the use of cytochrome P450 enzyme inducers (i.e., rifampin, phenobarbital, carbamazepine, phenytoin) with OTEZLA is not recommended [see Drug Interactions (7.3) and Clinical Pharmacology (12.3)].

ADVERSE REACTIONS: 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.

Psoriatic Arthritis Clinical Trials: OTEZLA was evaluated in 3 multicenter, randomized, double-blind, placebo-controlled trials (Studies PA-1, PA-2, and PA-3) of similar design in adult patients with active psoriatic arthritis [see Clinical Studies (14.1)]. Across the 3 studies, there were 1463 patients randomized equally to placebo, OTEZLA 20 mg twice daily or OTEZLA 30 mg twice daily. Titration was done over the first 5 days (see Dosage and Administration (2.1)). Placebo patients whose tender and swollen joint counts had not improved by at least 20% were re-randomized 1:1 in a blinded fashion to either OTEZLA 20 mg twice daily or OTEZLA 30 mg twice daily. Titration was done over the first 5 days (see Dosage and Administration (2.1)). OTEZLA were 1.8% (48/2510) of patients taking OTEZLA daily and 1.2% for placebo-treated patients.

Adverse Reactions Reported in 22% of Patients on OTEZLA 30 mg Twice Daily and 21% Than That Observed in Patients on Placebo On Day 1-6 (Placebo %, OTEZLA %):

Diarrhea (1.2%, 5.3%), Nausea (1.4%, 7.6%), Upper respiratory tract infection (0.6%, 8.6%), Vomiting (0.4%, 0.8%), Nasopharyngitis (0.2%, 5.2%), Abdominal pain upper (0.9%, 3.6%).

Adverse Reactions Reported in 22% of Patients on OTEZLA 30 mg Twice Daily and 21% Than That Observed in Patients on Placebo On Day 6-112 (Week 16) (Placebo %, OTEZLA %):

Diarrhea (1.6%, 7.7%), Nausea (3.1%, 6.8%), Headache (2.2%, 5.5%), Upper respiratory tract infection (1.8%, 3.8%), Vomiting (0.4%, 3.2%), Nasopharyngitis (1.6%, 2.6%), Abdominal pain upper (0.2%, 2.0%).

Of the reported gastrointestinal adverse reactions, 1 subject experienced a serious adverse reaction of nausea and vomiting in OTEZLA 30 mg twice daily. 1 subject treated with OTEZLA 20 mg twice daily experienced a serious adverse reaction of diarrhea. 1 patient treated with OTEZLA 30 mg twice daily experienced a serious adverse reaction of headache. Of the reported adverse drug reactions none were serious.

Other adverse reactions reported in patients on OTEZLA in clinical studies including extension studies:

Immune system disorders: Hypersensitivity: Investigations: Weight decrease, Gastrointestinal Disorders: Frequent bowel movement, gastroesophageal reflux disease, Dyspepsia, Metabolism and Nutritional Disorders: Decreased weight, Thrombosis, and Mediastinal Disorders: Cough, Skin and Subcutaneous Tissue Disorders: Rash

Other adverse reactions reported in patients on OTEZLA in clinical studies including extension studies:

OVERDOSAGE

In cases of overdose, patients should seek immediate medical help. Patients should be managed by symptomatic and supportive care should there be an overdose.

Manufactured for: Celgene Corporation, Summit, NJ 07901

OTEZLA® (apremilast) tablets, for oral use

RX Only

Based on APRPI.006 OTZ_PsaPsO_HCP_BSv.006 06_2017

©2014-2017 Celgene Corporation All Rights Reserved

CT03428_029-033 AD Otezla.indd 32

3/25/20 8:32 AM
Potential first-line treatment for advanced cSCC

ILIYA PETROU, M.D. | Staff Correspondent

The epidermal growth factor receptor inhibitor cetuximab has recently proven to be a viable alternative to treating advanced cutaneous squamous cell carcinoma tumors.

A retrospective study evaluated the clinical outcomes of cetuximab monotherapy.

The primary endpoint was the disease control rate at six weeks.

Results confirm efficacy as a first-line agent in advanced SCC cases and demonstrate an acceptable tolerance among patients.

The epidermal growth factor (EGFR) inhibitor cetuximab (Erbitux, Eli Lilly) achieved good outcomes in patients with advanced SCC, according to results of a recent study.1

Following basal cell carcinoma, cutaneous SCC is the most common skin cancer in western countries and their incidence remains on a steady rise. Some of the risk factors for SCC include chronic sun exposure, skin that is sensitive to ultraviolet radiation, and immunosuppression, which, in part, can explain why the geriatric population is more susceptible to developing this type of nonmelanoma skin cancer.

The recent multicenter study headed by Henri Montaudie, M.D., from the department of dermatology, University Hospital of Nice, Nice, France, found the monoclonal antibody cetuximab to be safe and effective for the treatment of advanced cutaneous SCC. In the retrospective study that included 58 patients (median age; 83.2 years) with advanced SCC, researchers evaluated the clinical outcomes of cetuximab administered as a monotherapy. The majority of patients (over 90%) were chemotherapy naïve and the median follow-up was 11.7 months. The primary endpoint was the disease control rate (DCR) at six weeks according to the RECIST (response evaluation criteria in solid tumors) criteria. Secondary endpoints included DCR at 12 weeks, objective response rate (ORR) at six and 12 weeks, progression-free survival (PFS), overall survival (OS), and safety profile.

Study outcomes showed that the DCR was 87% and 70% at six and 12 weeks, respectively, while the ORR was 53% and 42% at six and 12 weeks, respectively. The median PFS and OS were 9.7 months and 17.5 months, respectively. Data showed that 51 patients (88%) experienced toxicity, and 67 adverse events related to cetuximab occurred, with the large majority of them (84%) having a severity of grade 1 or 2.

“Cetuximab proves to be safe and efficient for the treatment of patients, even elderly ones, with advanced cutaneous SCC. These results indicate that cetuximab is a promising agent to test in new combinations, especially with immune checkpoint inhibitors such as anti-PD-1 agents,” wrote Henri Montaudie, M.D., and colleagues, in the study recently published in OncoTarget.

The vast majority of SCC lesions are treated with surgical resection and have a cure rate exceeding 90 percent in early-stage disease. In stark contrast however, the 5-year overall survival rate is below 50 percent for patients with local lymph node metastases and less than 10 percent for those with distant metastases. In the study recently published in OncoTarget, the disease control rate was 9.7 months and 17.5 months, respectively. The median PFS and OS were 9.7 months and 17.5 months, respectively.

As a monotherapy, the majority of patients (over 90%) were chemotherapy naïve and the median follow-up was 11.7 months. The primary endpoint was the disease control rate (DCR) at six weeks according to the RECIST (response evaluation criteria in solid tumors) criteria. Secondary endpoints included DCR at 12 weeks, objective response rate (ORR) at six and 12 weeks, progression-free survival (PFS), overall survival (OS), and safety profile.

Study outcomes showed that the DCR was 87% and 70% at six and 12 weeks, respectively, while the ORR was 53% and 42% at six and 12 weeks, respectively. The median PFS and OS were 9.7 months and 17.5 months, respectively. Data showed that 51 patients (88%) experienced toxicity, and 67 adverse events related to cetuximab occurred, with the large majority of them (84%) having a severity of grade 1 or 2.

“Cetuximab proves to be safe and efficient for the treatment of patients, even elderly ones, with advanced cutaneous SCC. These results indicate that cetuximab is a promising agent to test in new combinations, especially with immune checkpoint inhibitors such as anti-PD-1 agents.”

Henri Montaudie, M.D., and colleagues
University Hospital of Nice, Nice, France

References
Hair loss treatment controversies, concerns

ILYA PETROU, M.D. | Staff Correspondent

The landscape of hair loss therapies has evolved, bringing with it some concern around appropriate treatment. It is important for clinicians to stay abreast with the latest data coming out of trials and individually consult their hair loss patients accordingly on a case by case basis, says Amy McMichael, M.D., professor and chair, department of dermatology, Wake Forest Baptist Medical Center, Winston-Salem, N.C., who recently spoke at the Orlando Dermatology Aesthetic and Clinical conference in Orlando.

“There is always going to be new data coming out in the hair world. Although the pace of the current research is limited by the lack of funding in this field, if we keep working on it and we band together with our data and get larger data sets, we’ll be able to talk about these things and make more sense for our patients,” Dr. McMichael says.

BIOTIN

Although the true utility of biotin has long been disputed, the supplement has been regularly included in product formulas for hair loss because it has been viewed as beneficial. Aside from the fact that it doesn’t work very well in hair loss treatment, Dr. McMichael says, the main reason clinicians have been discouraging their patients from taking biotin supplements for their hair loss is the potential danger it can pose in medical testing.

Biotin is regularly used in assays in hormonal laboratory testing, including thyroid testing, hormone tests for pregnancy, as well as tests for cardiac arrest. As such, patients who are taking biotin supplements could have false test results if their laboratory test assay contained biotin.

“If you have a candid conversation with your patients, you can potentially avoid recommending the hair loss medication to those who may be potentially more at risk for this issue.”

Amy McMichael, M.D.
Wake Forest Baptist Medical Center,
Winston-Salem, N.C.

According to Dr. McMichael, the larger and growing concern is the effect that supplementary biotin can have on important medical testing that patients may be undergoing by obscuring results and, therefore, appropriate therapy.

JAK INHIBITORS

Continued research has led to an array of JAK inhibitors currently available for the treatment of alopecia areata. Clinicians need to know how and when to implement them appropriately. According to Dr. McMichael, it can be challenging to decide which patients should receive JAK inhibitor therapy, particularly when confronted with the explosion in therapeutic choices.

“I would recommend JAK therapy for older adolescents as well as adults, particularly those patients with a greater than 50% hair loss. We currently do not have any data on JAK inhibitors in children and, until that time comes, they should not be used in this patient population,” Dr. McMichael says.

Unfortunately, reimbursement can also be a limiting factor for many alopecia areata patients, but according to Dr. McMichael, those patients who have gone through a failed oral methotrexate treatment may have a higher likelihood of getting JAK inhibitor therapy approved by insurance companies.

5-ARI THERAPY

Though having proven efficacy in male pattern hair loss, 5-alpha-reductase inhibitor (5-ARI) therapy has been associated with some potential side effects including persistent erectile dysfunction (PED) and depression, as well as an increased risk for type 2 diabetes in male patients on the medication.

One recent study addressed the incidence of PED in a cohort of 12,000 male pattern baldness patients taking 5-ARIs (either finasteride or dutasteride) and found that 1.4% had PED.
Microneedling plus radiofrequency effective

CHERYL GUTTMAN KRADER, B.S. PHARM | Staff Correspondent

Microneedling with radiofrequency can be a valuable addition to a dermatologic practice because it effectively treats a variety of skin aging signs and other defects both on and off the face with minimal risk and downtime compared with alternative options, according to Glynis R. Ablon, M.D., who spoke at the 18th annual South Beach Symposium, Miami. Dr. Ablon says microneedling with radiofrequency is a great option for skin tightening and resurfacing to treat wrinkles, lip lines, acne scars, other depressed scars, and stretch marks, and it can be used regardless of skin phototype.

“One of the great things about microneedling with radiofrequency is that it is color blind. Unlike with lasers, microneedling with radiofrequency delivers energy in a way that is not chromophore dependent. Therefore, it is safe to use in patients with darker skin types,” says Dr. Ablon, associate clinical professor of dermatology, David Geffen School of Medicine at UCLA, Los Angeles, Calif., and founder and director, Ablon Skin Institute & Research Center, Manhattan Beach, Calif.

“In addition, because microneedling with radiofrequency has good depth control and delivers energy directly into the target area without loss of energy it can be used with greater safety to treat certain problems that would otherwise require an aggressive laser or peel resurfacing procedure,” she says.

She adds, however, that achieving optimal outcomes can require multiple sessions. “I tell patients they typically will need three or four treatments to achieve the best results. One of the biggest mistakes that clinicians make when using this technology is that they tell patients they will only need one session,” Dr. Ablon says. Depending on the patient’s presentation, a combination approach incorporating other treatment modalities may also be preferred. Microneedling with radiofrequency can be combined with a variety of other treatments, including platelet-rich plasma injections, resurfacing lasers, chemical peels, and subcision.

Providing an example, Dr. Ablon says that when treating a patient for acne scars, she will use a 100% trichloroacetic acid peel to address deep icepick scars and then use microneedling with radiofrequency on surrounding skin and scars.

MINIMAL MORBIDITY
Setting appropriate expectations for post-treatment sequelae is important for achieving patient satisfaction. The type and severity of postprocedural reactions and the duration of downtime depend on the nature of the treatment, Dr. Ablon says.
INDICATIONS AND USAGE
AMZEEQ™ (minocycline) topical foam, 4% is indicated for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in adults and pediatric patients 9 years of age and older.

Limitations of Use: This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, AMZEEQ should be used only as indicated.

IMPORTANT SAFETY INFORMATION
Contraindications: Persons who have shown hypersensitivity to any of the tetracyclines or any other ingredient in AMZEEQ.

Warnings and Precautions
Flammability: The propellant in AMZEEQ is flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application.

AMZEEQ is a topical foam. While systemic absorption of AMZEEQ is low, and serious adverse reactions were not seen in clinical studies, the following adverse reactions associated with oral minocycline should be considered:

Limitations of Use: This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, AMZEEQ should be used only as indicated.

IMPORTANT SAFETY INFORMATION (cont.)
• Teratogenic effects, inhibition of bone growth & permanent tooth discoloration: Use during the second and third trimesters of pregnancy, infancy and childhood up to the age of 8 years may cause permanent discoloration of the teeth (yellow-gray-brown) and reversible inhibition of bone growth.

Hepatotoxicity & metabolic effects: If renal impairment exists or if liver injury suspected, discontinue AMZEEQ. CDAD occurs, discontinue AMZEEQ.

Central nervous system effects: Patients experiencing light-headedness, dizziness or vertigo should be cautioned about driving vehicles or operating heavy machinery.

Intracranial hypertension: Clinical manifestations include headache, blurred vision, diplopia, and vision loss. Discontinue AMZEEQ immediately if symptoms occur.

Autoimmune syndromes: Symptoms may be manifested by fever, rash, arthralgia, and malaise. Discontinue AMZEEQ immediately if symptoms occur.
THE FIRST AND ONLY TOPICAL MINOCYCLINE

The minocycline you know and trust.¹
• In large, 12-week trials, Amzeeq demonstrated an improvement vs. vehicle foam in both inflammatory lesions and IGA scores.³⁴
• The most commonly reported adverse reaction was headache (3%).¹²

The tolerability of a gentle foam.¹
• Proprietary oil-based foam vehicle contains natural moisturizing ingredients without drying agents like ethyl alcohol.¹³¹

The innovation you’ve been waiting for.
• Molecule Stabilizing Technology (MST)™ enables minocycline to be placed into a lipophilic vehicle for stable topical delivery.¹⁴⁵

IMPORTANT SAFETY INFORMATION (cont.)

• Photosensitivity: Patients should minimize or avoid exposure to natural or artificial sunlight while using AMZEEQ. Advise patients to discontinue treatment with AMZEEQ at the first evidence of sunburn.
• Hypersensitivity reactions: Discontinue AMZEEQ immediately if symptoms of anaphylaxis, serious skin reactions, erythema multiforme, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome occur.
• Tissue hyperpigmentation: Discoloration of organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclerae and heart valves.
• Superinfection: Overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue AMZEEQ and institute appropriate therapy.

Adverse Reactions: The most common adverse reaction reported during clinical trials of AMZEEQ was headache.

* Coprimary endpoints at Week 12 were Absolute change from baseline in inflammatory lesion count and IGA endpoint success. IGA success was defined as an IGA score of 0 or 1 (clear or almost clear), and at least a 2-grade improvement (decrease). IGA = Investigator’s Global Assessment. 2418 patients were included if they had 20-50 inflammatory lesions (papules, pustules, nodules) and 25-100 noninflammatory lesions (open, closed comedones) and an IGA score on a 6-point scale of moderate or severe (grade 3 or 4).
† Amzeeq 4% topical foam contains the following inactive ingredients: soybean oil, coconut oil, light mineral oil, cyclomethicone, cetostearyl alcohol, stea ric acid, myristyl alcohol, hydrogenated castor oil, white wax (beeswax), stearyl alcohol, docosanol, and propellants (butane + isobutane + propane).


See Brief Summary of Prescribing Information for AMZEEQ on following pages.

Amzeeq is a trademark of Foamix Pharmaceuticals © 2020 Foamix Pharmaceuticals. All rights reserved. COM-AMZ-US-200085 2/2020
AMZEEQ™ (minocycline) topical foam, 4% BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION. PLEASE SEE FULL PRESCRIBING INFORMATION.

INDICATION AMZEEQ is indicated for the topical treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in adults and pediatric patients 9 years of age and older.

Limitations of Use: This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, AMZEEQ should be used only as indicated.

CONTRAINDICATIONS This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines or any other ingredients within AMZEEQ.

WARNINGS AND PRECAUTIONS

- **Flammability:** The propellant in AMZEEQ is flammable. Instruct the patient to avoid fire, flame, or smoking during and immediately following application. Do not puncture and/or incinerate the containers. Do not expose containers to heat and/or store at temperatures above 120°F (49°C).
- **Tetracyclen Effects:** Minocycline, like other tetracycline-class drugs, may inhibit bone growth when administered orally during pregnancy. Based on animal data, when administered orally, tetracyclines cross the placenta, are found in fetal tissues, and can cause skeletal malformation and retardation of skeletal development on the developing fetus.
- **Tooth Discoloration:** The use of tetracycline class drugs orally during tooth development (second and third trimesters of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term oral use of the tetracycline but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported with oral tetracycline drugs. Use of tetracycline drugs is not recommended during tooth development. The safety and effectiveness of AMZEEQ have not been established in pediatric patients less than 9 years of age.
- **Inhibition of Bone Growth:** All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in premature human infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. The safety and effectiveness of AMZEEQ have not been established in patients less than 9 years of age. Results of animal studies indicate that oral tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development on the developing fetus.
- **Clostridium difficile Associated Diarrhea:** Clostridium difficile associated diarrhea (CDAD) has been reported with nearly all antibacterial agents, including oral minocycline, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxic producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.
- **Hepatotoxicity:** Post-marketing cases of serious liver injury, including irreversible drug-induced hepatitis and fulminant hepatic failure (sometimes fatal) have been reported with oral minocycline use in the treatment of acne.
- **Metabolic Effects:** The anti-anabolic action of the tetracyclines may cause an increase in blood urea nitrogen (BUN). In patients with significantly impaired function, higher serum levels of tetracycline-class drugs may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, recommended oral or parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, adjust the dose downward, and if therapy is prolonged, serum level determinations of the drug may be advisable.
- **Central Nervous System Effects:** Central nervous system side effects including light-headedness, dizziness or vertigo have been reported with oral minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and may disappear when the drug is discontinued.
- **Intracranial Hypertension:** Intracranial hypertension has been associated with the use of tetracycline-class drugs. Clinical manifestations of intracranial hypertension include headache, blurred vision, diplopia and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH at risk are at a greater risk for developing intracranial hypertension. Patients should be questioned for visual disturbances prior to initiation of treatment with tetracyclines. Concomitant use of isotretinoin and tetracycline should be avoided because isotretinoin, a systemic retinoid, is also known to cause intracranial hypertension. Although intracranial hypertension typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Because intracranial pressure can remain elevated for weeks after drug cessation, patients should be monitored until they stabilize.
- **Autoimmune Syndromes:** Tetracyclines have been associated with the development of autoimmune syndromes. The long-term use of oral minocycline in the treatment of acne has been associated with drug-induced lupus-like syndrome, autoimmune hepatitis and vasculitis. Sporadic cases of serum sickness have presented shortly after oral minocycline use. Symptoms may be manifested by fever, rash, arthritis, and malaise. In symptomatic patients, immediately discontinue the use of all tetracycline-class drugs, including AMZEEQ.
- **Photosensitivity:** Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking oral tetracyclines; this reaction has been reported less frequently with minocycline. Although AMZEEQ did not induce phototoxicity or photoallergic responses in human dermal safety studies, patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UV/A/B treatment) while using minocycline. If patients need to be outdoors while using AMZEEQ, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. Advise patients to discontinue AMZEEQ treatment with AMZEEQ at the first evidence of sunburn.
- **Serious Skin/Hypersensitivity Reaction:** Cases of anaphylaxis, serious skin reactions (e.g. Stevens Johnson syndrome, erythema multiforme), and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been reported postmarketing with oral minocycline use in patients with acne. DRESS syndrome consists of cutaneous reactions (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following visceral complications such as: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. Fever and lymphadenopathy may be present. In some cases, death has been reported with oral minocycline use. If this syndrome is recognized, discontinue AMZEEQ immediately.
- **Tissue Hyperpigmentation:** Oral tetracyclines are known to cause hyperpigmentation. Tetracycline therapy may induce hyperpigmentation in many organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclera and heart valves. Skin and oral hyperpigmentation has been reported to occur independently of time or amount of drug administration, whereas other tissue pigmentation has been reported to occur upon prolonged administration. Skin pigmentation includes diffuse pigmentation as well as pigmentation over sites of scars or injury.

- **Development of Drug-Resistant Bacteria: AMZEEQ has not been evaluated in the treatment of infections. Bacterial resistance to the tetracyclines may develop in patients using AMZEEQ, therefore, the susceptibility of bacteria associated with infection should be considered in selecting antimicrobial therapy. Because of the potential for drug-resistant bacteria to develop during the use of AMZEEQ, it should be used only as indicated.

- **Superinfection/Potential for Micobacterial Overgrowth:** Use of AMZEEQ may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue AMZEEQ and institute appropriate therapy.

ADVERSE REACTIONS

- **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 practice. In 3 randomized, double-blind, vehicle-controlled trials, subjects age 9 years and older applied AMZEEQ or vehicle once daily for 12 weeks. A total of 1,356 subjects were treated with AMZEEQ and 1,058 with vehicle. The majority of subjects were White (74%) and female (60%). Approximately 34% were Hispanic/Latino and 49% were younger than 18 years of age.

- **The most common adverse reaction reported by ≥1% of subjects treated with AMZEEQ and more frequently than in subjects treated with vehicle was**
headache, which was reported in 3% of subjects treated with AMZEEQ and 2% of subjects treated with vehicle. Local tolerability evaluations were conducted at each study visit in the clinical trial by assessment of erythema, dryness, hyperpigmentation, skin peeling and itching. The active assessment of the signs and symptoms of local facial tolerability at Week 12 in subjects treated with AMZEEQ was as follows (mild, moderate, severe): erythema (14.2%, 1.5%, 0%), dryness (6.8%, 0.6%, 0%), hyperpigmentation (12.4%, 2.8%, 0.1%), skin peeling (3.2%, 0.2%, 0%), and itching (5.1%, 0.8%, 0.1%). Hyperpigmentation was most frequently assessed as characteristic of inflammatory and post-inflammatory changes associated with acne. Local tolerability signs and symptoms occurred in similar frequency and severity as subjects treated with the vehicle component of AMZEEQ. In a 40-week open-label extension safety study (for a total of up to 52 weeks of treatment), frequency and severity of local tolerability signs and symptoms at Week 52 were comparable to those reported at Week 12.

DRUG INTERACTIONS

- **Anticoagulants:** Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.
- **Penicillin:** Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.
- **Drug/Laboratory Test Interactions:** False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Risk Summary: Available data with AMZEEQ use in pregnant women is insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Systemic absorption of AMZEEQ in humans is low following once daily topical administration of AMZEEQ for 21 days. Because of low systemic exposure, it is not expected that maternal use of AMZEEQ will result in significant fetal exposure to the drug. Tetracycline-class drugs may cause permanent discoloration of teeth and reversible inhibition of bone growth when administered orally during pregnancy. Animal reproduction studies were not conducted with AMZEEQ. In animal reproduction studies, oral administration of minocycline administered to pregnant rats and rabbits during the period of organogenesis induced skeletal malformations in fetuses at systemic exposures of 750 and 500 times, respectively, the maximum recommended human dose (MRHD; based on AUC comparison) of AMZEEQ (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 birth defect, loss, or 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:** Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development of the developing fetus. Minocycline induced skeletal malformations (bent limb bones) in fetuses when orally administered to pregnant rats and rabbits during the period of organogenesis at doses of 30 mg/kg/day and 100 mg/kg/day, respectively, (750 and 500 times, respectively, the systemic exposure at the MRHD based on AUC comparison). Reduced mean fetal body weight was observed when minocycline was orally administered to pregnant rats during the period of organogenesis at a dose of 10 mg/kg/day (250 times the systemic exposure at the MRHD based on AUC comparison).
- **Minocycline** was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats during the period of organogenesis through lactation, at doses of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (650 times the systemic exposure at the MRHD based on AUC comparison). No effects of treatment on the duration of the gestation period or the number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received oral minocycline) included reduced body size, improperly rotated forelimbs, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).
- **Lactation:** Risk Summary: Tetracycline-class drugs, including minocycline, are present in breast milk following oral administration. It is not known whether minocycline is present in human milk after topical administration to the nursing mother. There are no data on the effects of minocycline on milk production. Because of the potential for serious adverse reactions, advise patients that breastfeeding is not recommended during treatment with AMZEEQ.

- **Pediatric Use:** The safety and effectiveness of AMZEEQ have been established in pediatric patients 9 years of age and older for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris. Use of AMZEEQ for this indication is supported by three adequate and well controlled 12-week trials in patients 9 years of age and older; two of the trials included a 40-week open-label extension. Additional data was obtained from a 7-day open-label safety and pharmacokinetics study conducted in 20 patients 10 years to less than 17 years of age with acne vulgaris. A total of 686 subjects 9 years of age and older received AMZEEQ in these clinical trials. Safety and effectiveness for this indication have not been established in pediatric patients less than 9 years of age. The use of oral tetracycline drugs during tooth development below the age of 8 years may cause permanent discoloration of the teeth (yellow-gray-brown) and inhibition of bone growth.
- **Geriatric Use:** Clinical studies of AMZEEQ did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

NONCLINICAL TOXICOLOGY

- **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a carcinogenicity study in which minocycline hydrochloride was orally administered to male and female rats once daily for up to 104 weeks at dosages up to 200 mg/kg/day, minocycline hydrochloride was associated with both sexes with follicular cell tumors of the thyroid gland, including increased incidences of adenomas, carcinomas and the combined incidence of adenomas and carcinomas in males, and adenomas and the combined incidence of adenomas and carcinomas in females. In a carcinogenicity study in which minocycline hydrochloride was orally administered to male and female mice once daily for up to 104 weeks at dosages up to 150 mg/kg/day, exposure to minocycline hydrochloride did not result in a significantly increased incidence of neoplasms in either males or females. Minocycline was not mutagenic in vitro in a bacterial reverse mutation assay (Ames test) or CHO/HGPRT mammalian cell assay in the presence or absence of metabolic activation. Minocycline was not clastogenic in vitro using human peripheral blood lymphocytes or in vivo in a mouse micronucleus test.

- **Male and female reproductive performance in rats was unaffected by oral doses of minocycline of up to 300 mg/kg/day (10,000 times the systemic exposure at the MRHD based on AUC comparison). However, oral administration of 100 or 300 mg/kg/day of minocycline to male rats (3,800 or 10,000 times, respectively, the systemic exposure at the MRHD based on AUC comparison), adversely affected spermatogenesis. Effects observed at 300 mg/kg/day of oral minocycline included a reduced number of sperm cells per gram of epididymis, an apparent reduction in the percentage of sperm that were motile, and (at 100 and 300 mg/kg/day) increased numbers of morphologically abnormal sperm cells. Morphological abnormalities observed in sperm samples included absent heads, misshapen heads, and abnormal flagella.

- **HANDLING:** Allow the can to warm to room temperature before first use. Shake can well before use.

- **WARNING:** Flammable. Avoid fire, flame, or smoking during and immediately following application. Contents under pressure. Do not puncture or incinerate. Do not expose to heat or temperatures above 49°C (120°F).

For more information, including the FDA-approved Prescribing Information, go to www.amzeeq.com or call 1-844-375-3673.

AMZEEQ is a trademark of Foamix Pharmaceuticals Ltd. All other trademarks are the properties of their respective owners.

Copyright © 2020, Foamix Pharmaceuticals Ltd. All rights reserved.
Hair loss treatment concerns  FROM PAGE 34

Interestingly, a closer look at the data showed that there was a moderate number of patients with PED who were toward the younger age spectrum (15-42 years).

“Though this is a very small number, it does raise the concern that you need to discuss the potentially pre-existent sexual dysfunction and depression in patients. People often think that because men are young, they do not have sexual dysfunction but that is not actually always true. If you have a candid conversation with your patients, you can potentially avoid recommending the hair loss medication to those who may be potentially more at risk for this issue,” Dr. McMichael says.

Another study addressed the concern of 5-ARIs and the patient’s risk for type 2 diabetes, where researchers found a small but not negligible trend for patients on the drug to develop the condition.

“Clinicians should carefully consult their patients and be mindful when considering 5 alpha reductase inhibitor medications in those patients who are at a higher risk of type 2 diabetes,” Dr. McMichael says.

Disclosures:
Dr. McMichael reports no relevant disclosures.

References:

Microneedling plus radiofrequency effective option for skin aging FROM PAGE 35

With mild treatments, patients generally experience no postoperative pain and little to no social downtime. Treatments performed with more aggressive parameters are associated with more sequelae, but generally patients only experience mild to moderate postoperative pain and minimal downtime.

“Most patients can return to work in a few days but they need to expect prepared to have visible prick marks on the skin that can persist for three to five days,” Dr. Ablon says.

A topical anesthetic is used to improve patient comfort during the procedure, although a nerve block may be used when treating around the mouth. To minimize complications, patients should be advised to avoid using any anti-inflammatory treatments for 2 weeks prior to the procedure and retinoids for three days.

To prevent herpes reactivation, patients who are being treated around the mouth are started on valacyclovir with dose adjustment as necessary for renal impairment. Due to the risk of folliculitis, valacyclovir along with an oral antibiotic are prescribed for all patients who are having a more aggressive treatment or who have a history of folliculitis with a previous treatment.

“To avoid complications, always maintain sterility throughout the procedure,” Dr. Ablon adds.

PURCHASING DECISIONS
With a number of devices on the market that differ in a variety of features, clinicians may wonder which system to choose. The first issue to consider, however, is whether microneedling with radiofrequency is a good fit for their practice, Dr. Ablon says.

“Think about the types of patients that you see. If your aesthetic focus is on hair removal, then a microneedling-radiofrequency system is not for you,” she says. “If you are looking to add services for acne scars, traumatic scars, wrinkles and/or laxity, then a microneedling device with radiofrequency is a great addition.”

The available systems vary in the type of needles they use, including whether the needles are insulated or not and whether they are variable or fixed lengths. Insulated needles are designed to protect the epidermis. They emit radiofrequency energy only at the tip and cause low volume heating.

“Because microneedling with radiofrequency has good depth control and delivers energy directly into the target area without loss of energy it can be used with greater safety to treat certain problems that would otherwise require an aggressive laser or peel resurfacing procedure.”

“With insulated needles, multiple passes (penetrations) are needed, and the associated trauma results in bleeding and subsequently more downtime for patients,” Dr. Ablon says.

Non-insulated microneedles are active along the entire length and cause high volumetric heating. “Because only a single pass is needed when using a system with non-insulated needles, treatments with non-insulated needles carry advantages for shorter procedure time, less trauma, and less downtime. However, I still typically proceed with three passes to achieve more dramatic results on the majority of my patients.”

Needle depth is an important consideration because penetration into the dermis is necessary to stimulate collagen production and tissue tightening, Dr. Ablon says.

She notes that her preference is for needles that can penetrate between 0.5 and 5.0 mm. She also likes needles that are gold-plated and tapered, which allows for smooth penetration through the epidermis and dermal-epidermal junction, thereby avoiding unnecessary trauma to the skin and minimizing the risk of pigmen-

tary changes with non-insulated needles

TREATMENT PARAMETERS
Skin thickness is a consideration for choosing appropriate settings. Dr. Ablon says that she uses a shorter pulse width and needle penetration depth when treating skin on the hands, the neck, or periorbital areas than for procedures on the cheeks or upper lip.

“For enhanced clinical effect it is possible to cover the area with additional passes of pulses, but do not stack pulses because stacking can lead to excess heating of tissue that could cause damage or burn,” she says.

“In addition, I may do two passes with radiofrequency and a third superficial pass with microneedling alone, setting the radiofrequency power to 0. This third pass without radiofrequency is working more superficially and so I do not need the heat as much as I want the collagen induction that can be gotten from the needling alone as well as the zones of trauma in the epidermis for more contraction.”

Disclosure:
Dr. Ablon is a speaker for Endymed and MTDerm and receives research grants from MTDerm.
COVID-19 pandemic requires vigilance, not panic

JOHN JESITUS | Staff Correspondent

As of mid-March, the national pandemic continued to escalate, with new cases and findings about the COVID-19 virus coming daily, revealing the implications on dermatology practice and patients. In combatting the pandemic, dermatologists must take critical steps to adapt operations while still providing essential patient care and preventing exposure in office settings, experts say.

Dermatologists are well-aware of the ability of viruses to cause regular cold symptoms, says Bobby Buka, M.D., cofounder of The Dermatology Specialists in New York. Covid-19, the infection caused by the SARS-CoV-2 virus, is similar in that regard.

“But the virulence of COVID-19 is more impressive than prior versions, and its mortality and morbidity rate is higher than its predecessors,” he says. As of March 25, the U.S. Centers for Disease Control (CDC) had tallied 737 fatal- ities among 54,453 cases, a 1.4% mortality rate.

In outpatient settings, Dr. Buka says, physicians may think that because COVID-19 is not a dermatologic condition, they won’t be on the frontlines.

“But in a pandemic situation, we’re all on the frontlines, and I trust my colleagues to be part of the unfolding efforts to control the spread of this virus,” he says.

In a message March 19, to members, George Hruza, M.D., outgoing president of the American Academy of Dermatology (AAD), shared the latest insight related to the dermatology specialty, which included guidance on self-protection, as well as the protection of staff and patients. Among the resources provided, were tips for patient screenings and effective disinfecting solutions for use around the clinic based on guidance from the Centers for Disease Control (CDC) and the World Health Organization (WHO). AAD is compiling all resources related to the pandemic for members, which can be found at www.aad.org/coronavirus.

As in other specialties, dermatologists’ practices have been verbally screening for viral exposure, ideally before patients enter a facility, says Ted Rosen, M.D., professor and vice chair of dermatology at Baylor College of Medicine, Houston.

“It is advisable to have schedulers screen anyone calling in for an appointment,” he says.

He suggests asking about symptoms of flu-like illness; travel in the past two weeks to international and domestic locations currently experiencing significant outbreaks; proximity to anyone subsequently diagnosed with coronavirus infection and recent participation in cruises.

Dr. Buka says, physicians may think that because COVID-19 is not a dermatologic condition, they won’t be on the frontlines.

“In a pandemic situation, we’re all on the frontlines, and I trust my colleagues to be part of the unfolding efforts to control the spread of this.”

Bobby Buka, M.D.
The Dermatology Specialists, New York

According to a February 18 New England Journal of Medicine report, out of 126 German travelers returning from China, one (who had passed symptom-based screening) subsequently tested positive for SARS-CoV-2 and was found to have a faint rash.

As SARS-CoV-2 is a coronavirus, says Dr. Buka, one might expect a sandpaper-like morbilliform eruption to impact 10% to 15% of patients. A classic leukocytic vasculitis presenting as purpuric or ecchymoses on the lower extremities could impact approximately 2% to 3% of patients, he adds.

Upper-respiratory infection (URI) symptoms — scratchy throat, mild fatigue and headache — typically precede dermatologic manifestations, says Dr. Buka. But in 80% to 90% of COVID-19 cases, he says, URI presentations are mild and may go unnoticed. The rash can occur either concomitantly with, or two to 14 days following URI symptoms, he says.

“That two- to 14-day range also corresponds with the incubation period of COVID-19, which means we can get exposure and the rash alongside the URI symptoms,” he suggests.

Recently, a patient presented to Dr. Buka with a girdle rash but no fever, which ruled out COVID-19.

“But,” he says “if we have fever and morbilliform rash, currently that’s going to be at the top of my differential. It can be helpful among the constellation of other symptoms to make an earlier diagnosis.”

However, Dr. Rosen says that although very few anecdotal reports indicate the presence of a poorly defined, faint morbilliform eruption with COVID-
Vigilance FROM PAGE 41

19, a skin rash is not considered characteristic; nor is it likely to be.

Older literature regarding viral exanthems are suspect, he adds, because diagnostic testing for viral diseases is much more sophisticated today.

Rodney E. Rohde, Ph.D., M.S., says that no solid evidence or peer-reviewed publications report issues with SARS-CoV-2/COVID-19 being transmitted to skin eruptions and similar dermatology symptoms. He is professor and chair of the Clinical Laboratory Sciences Program at Texas State University. He also serves as a research dean for the College of Health and associate director of the Translational Health Research Center at the University.

“If these skin eruptions/rashes are an early sign of COVID-19,” he says, “then that certainly could be used as a possible screening tool for testing — and diligent PPE (use) for healthcare workers of all walks.”

PUBLIC HEALTH MEASURES

Local emergency declarations, cancellations and social distancing are all effective, time-tested public measures for containing or attempting to stop microbe outbreaks, Dr. Rohde says. While people understand the critical importance of handwashing, physicians and officials must raise awareness of high-touch surfaces because SARS-CoV-2/COVID-19 (and other microbes) can remain viable for several hours on touch surfaces because SARS-CoV-2/Covid-19 (and other microbes) can remain viable for several hours on touchscreens, handrails and elevator buttons.

The World Health Organization recommends wiping down all chairs and arm rests, exam room tables, counters, doorknobs, light buttons and handles, faucet handles, all bathroom surfaces, reception area counters, all lab surfaces, and all kitchen area surfaces; keep trash cans empty and wipe down the inside and outside of containers regularly and thoroughly.

In the coming weeks, Dr. Buka anticipates seeing fewer patients overall as people have increasing trepidation about leaving their homes. Dr. Rosen adds that some patients who sought face-to-face encounters for skin issues are requesting “virtual” visits, real-time or otherwise.

Physicians looking to leverage telemedicine technology with patients exhibiting respiratory symptoms requiring dermatology care may be able to now receive reimbursement from Medicare, according to the AAD, which offers help with getting started and assistance with coding through its membership resources.

With no vaccine presently available, says Dr. Rohde, the number of U.S. cases will almost inevitably rise. That will mean federal government support will become more important, but it doesn’t mean people should panic, he says.

Dr. Rosen emphasizes that most patients affected by COVID-19 will have mild disease and completely recover. It is the elderly patient with underlying chronic disease who is at highest risk for severe disease.

“We all, as healthcare providers, should emphasize the commonplace and simple precautions that our patients can take to mitigate the risk, and try to de-emphasize doom-and-gloom predictions of apocalyptic disaster. There’s too much hysteria already.”

As of this publication, Dr. Huza has appointed an Ad Hoc Task Force to assess the specialty’s needs, share new information, and provide ongoing guidance and information, which can be found on the AAD website. *

References:


Disclosures:

Dr. Buka, Rohde and Rosen report no relevant financial interests.

AAD ISSUES BIOLOGIC GUIDANCE

By Heather Onorati

EXPERTS HAVE ADVISED that those of greatest risk exposed to Covid-19 are those who are older, have underlying medical conditions or who are immuno-compromised. The question then is how to manage patients on immunomodulatory therapies for their dermatologic conditions. While there is no data on which to base guidelines, the American Academy of Dermatology (AAD) has issued interim recommendations for practitioners to balance the risk of immunosuppression with the risk of disease flare.

“A main priority for dermatologists, of this point, is to keep our patients’ out of emergency rooms and urgent care so as not to tax the healthcare system unnecessarily,” the statement, issued March 18, reads.

According to AAD’s current guidance, dermatologists are advised to keep patients on their biologic therapy. They have not tested positive or do not exhibit signs of symptoms of COVID-19. According to AAD, there is currently insuffi-

cient data to recommend discontinuing therapy. Howev-
er, physicians are advised to actively discuss the risks and benefits with their patients, weighing the severity of the patient’s indication for therapy, the patient’s age and any comorbidities that would place the patient at high risk for serious illness should they be exposed to the virus.

If a patient has tested positive for COVID-19, physicians should follow the guidelines for managing patients on biologics with active infections and discontinue or postpone the start of therapy until the patient recovers. AAD recommends that a patient is a candidate for biologic therapy. AAD recommends physicians assess the individual risk vs. benefit profile of treatment in patients at low-risk for serious illness from COVID-19. If a patient is in a high-risk population, it may be more prudent to utilize alternative therapeutic approaches and delay biologic initiation at this time.

You can find this guidance and more at www.aad.org/coronavirus. *
closely with the scientific community around the world and several clinical trials are underway.

Among the most highlighted of the potential candidates, has been the anti-malaria drug, hydroxychloroquine (HCQ, Plaquenil), which experts and the president have highlighted for both post-exposure prophylaxis and treatment of COVID-19.

In a recent post on the Maui Derm for Dermatologists event site, George Martin, M.D., program director, along with colleagues Ted Rosen, M.D., Sheila Fallon-Friedlander, M.D., Albert Yan, M.D., and James Treat, M.D., shared summaries of data that provide evidence of the drug’s use, dosing, as well as epidemiology of COVID-19 infections (bit.ly/MauiDermHCQdata). The single best epidemiology modeling data, they note, is a commentary published on the website Medium, that shows the speed at which the virus is replicating around the world, and it is with this urgency in mind that they compiled what they viewed as the most impressive data they say may save lives.

“The number of cases reported daily grossly underestimates the true number of cases and many asymptomatic but infected individuals are unknowingly spreading the disease,” Dr. Rosen says in the summary.

Isolated quarantines will likely be insufficient, Dr. Martin says. According to a letter they cite, which was published in the New England Journal of Medicine, March 17, 2020, the virus remained stable on various surfaces for several days. The virus had the ability to remain airborne for up to three hours, and it could survive on plastic for up to three days and on steel for up to two days.

HCQ is a drug already approved by the FDA for the treatment of malaria, discoid and lupus erythematosus and rheumatoid arthritis. Therefore, it may be prescribed off-label.

While President Donald Trump announced March 19 that he’s pushing FDA to eliminate barriers to make HCQ available, FDA Commissioner Stephen Hahn says the organization will remain responsible in its evaluation of potential therapeutic options, including those that are already approved for other indications, “to make sure that patients receive the right dosage at the right time,” according to CNN politics.

Following the president’s comments that HCQ could treat COVID-19 and a series of studies indicating its potential benefit, hospitals began purchasing large quantities, pharmacists reported depleted supplies and manufacturers reported back orders.

“As a result of hydroxychloroquine and chloroquine being explored as a potential treatment for COVID-19, patients currently taking these medications are having difficulties filling their prescriptions and manufacturers reported back orders. As investigations continue, recent data from a small study of 30 patients, reported March 24, by Bloomberg News, showed that hydroxychloroquine was no more effective than managing patient symptoms conventionally.

The study, which was conducted by researchers from the department of infection and immunity at the Shanghai Public Health Clinical Center, involved 15 patients treated with hydroxychloroquine and 15 controls who were managed with bed rest, oxygen inhalation, anti-viral drugs recommended in China’s treatment guidelines, and antibiotics when necessary. Of the 15 patients treated, 13 tested negative after one week of treatment vs. 14 patients in the control group who were managed conventionally. One patient in the treatment group progressed to severe disease and four patients developed diarrhea and signs of possible liver damage. The researchers concluded that a larger-scale investigation is required to better understand the drug’s benefit and risk profile.

“Our scientific clinical trials data is not as robust as the media attention,” Dr. Ehrlich says. “We are already seeing some of the dangers of unsupervised use as witnessed in toxicity cases in Nigeria (3 patients) and Arizona (2 patients).”

She adds that while chloroquine and hydroxychloroquine are generally safe when dosed correctly, the clinical trials data is still limited for this indication. The studies that have supported recommendations for the drug’s use in the treatment of the current pandemic are not high-quality, well-controlled studies.

According to Dr. Ehrlich, several other drugs being studied are interesting. For example, “IL-6 blocking agents may have a role in decreasing pulmonary inflammation,” she says. Interleukin-6 (IL-6) may play a role in driving the overactive inflammatory response in the lungs of patients who are critically ill with COVID-19.

Regeneron and Sanofi have initiated a phase 2/3 clinical trial evaluating the IL-6 inhibitor sotrovimab (Preccizumab (Actemra, Genentech) to evaluate its safety and efficacy in combination with standard of care in hospitalized adult patients with severe COVID-19 pneumonia. Tocilizumab is an IL-6 receptor agonist approved for the treatment of rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis.

Finally, remdesivir (Gilead), an investigational monophosphoramidate prodrug of an adenosine analog that was developed in response to the 2014-2016 Ebola outbreak, is being investigated. There are four clinical trials enrolling patients in the United States. The drug was available for compassionate use until the company suspended that access due to overwhelming demand. Gilead expects to set up a broader access program, but critically ill patients are now left in limbo.

The bottom line, says Dr. Ehrlich: “We just don’t have really strong clinical trial data yet. Until we have strong clinical trial data to support specific therapies for Covid-19, it’s going to be very challenging.”

Dr. Rosen comments, “At this point in time, social distancing is the most effective way we can combat the spread of COVID-19. Any way you can contribute to that concept will be of value, including reducing the number of patients coming for face-to-face office visits. Postpone elective procedures, delay return visits for stable established patients and practice teledermatology in any way and as often you can.”

For more information:
www.dermatologytimes.com/coronavirus
www.aad.org/coronavirus
bit.ly/MauiDermHCQdata
Partner with a leader that has 40+ years of authority and trust in dermatology.

Contact me to place your ad today.

Joanna Shippoli
(440) 891-2615
jshippoli@mjlifesciences.com

### AD INDEX

<table>
<thead>
<tr>
<th>ADVERTISER</th>
<th>PRODUCT</th>
<th>WEBSITE</th>
<th>PAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amgen</td>
<td>Otezla</td>
<td>otezilopro.com</td>
<td>29–32</td>
</tr>
<tr>
<td>Silverberg Podcast</td>
<td></td>
<td>dermatologytimes.com/atoropicdermatitis</td>
<td>14</td>
</tr>
<tr>
<td>Cosmetic Surgery Forum</td>
<td></td>
<td>cosmeticsurgeryforum.com</td>
<td>27</td>
</tr>
<tr>
<td>Dermatology Foundation</td>
<td></td>
<td>dermatologyfoundation.org</td>
<td>4–6</td>
</tr>
<tr>
<td>Foanix</td>
<td></td>
<td>amzeehcp.com</td>
<td>36–39</td>
</tr>
<tr>
<td>Galderma</td>
<td>Akleif</td>
<td>akleif.com/HCP</td>
<td>cover tip</td>
</tr>
<tr>
<td>Galderma</td>
<td>Epiduo</td>
<td>epiduoforte.com/hcp</td>
<td>CV2–1</td>
</tr>
<tr>
<td>Galderma</td>
<td>Oracea</td>
<td>rosacearelief.com</td>
<td>CV4</td>
</tr>
<tr>
<td>LeoPharma</td>
<td></td>
<td>enstilar.com</td>
<td>17–19</td>
</tr>
<tr>
<td>Ortho Dermatologics LLC</td>
<td>Siliq</td>
<td>siliq.com</td>
<td>insert 24–25</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Abrocitinib</td>
<td>pfizer.com</td>
<td>insert 40–41</td>
</tr>
</tbody>
</table>

This index is provided as an additional service. The publisher does not assume any liability for errors or omissions.
The Department of Dermatology at Penn State Health Milton S. Hershey Medical Center is seeking a full-time Dermatologist to join our practice in State College, PA.

Position Highlights:
• Appointment will be at the Assistant or Associate Professor level
• Join a growing and busy academic practice
• Large primary care referral base
• Highly collaborative culture
• Faculty rank commensurate with experience
• Competitive salary and generous benefits

Position Requirements:
• M.D., M.D./Ph.D. or equivalent degree
• BE/BC Dermatology
• A strong commitment to patient care and education. Research interests not required

Community:
• State College, PA is home to Pennsylvania State University & University Park, which is the largest campus in the Penn State system.
• State College is more than just a quintessential college town. It is vibrant with exciting nightlife, great shopping, many options for arts & culture, and a diverse array of restaurants.
• State College Area School District ranks in the top 100 school districts in the State of Pennsylvania.
• Nestled at the base of Mount Nittany, State College is a unique and wonderful combination of small town charm and college town action that makes it no surprise that this area of central Pennsylvania is known as “Happy Valley.”

Penn State Health:
• Penn State Health is a multi-hospital health system serving patients and communities across central Pennsylvania.
• More than 1,300 physicians and direct care providers at 78 medical office locations.

FOR MORE INFORMATION PLEASE CONTACT:
Jeffrey J. Miller, MD, MBA
Professor and Chair, Department of Dermatology
Penn State Health Milton S. Hershey Medical Center
c/o Erica Geist | Physician Recruiter
egeist@pennstatehealth.psu.edu

Penn State Health is committed to affirmative action, equal opportunity and the diversity of its workforce. Equal Opportunity Employer – Women/Minorities/Disabled/Veterans.

Contact Dan at (561) 286-4804
or DSchueller@mydermgroup.com