The Dermatology Therapeutic Landscape: New and Emerging Options

From new developments in psoriasis to atopic dermatitis and beyond, dermatology anticipates a number of emerging treatments.

BY NEAL BHATIA, MD

>> It's hard to believe that just over a decade ago, dermatologists were fretting over a paucity of new chemical entities coming to market for diseases of the skin, hair, and mucous membranes. The biologic revolution has continued and expanded, and we have seen new small molecules enter the space, as well as promising topical treatments. Here's a look at some of the latest and promising treatments in the dermatology pipeline.

Sofpironium bromide

Sofpironium bromide is a new chemical entity in development (Brickell Biotech) as a potent self-administered, once-daily, topical therapy for the treatment of primary axillary hyperhidrosis. An NDA is expected to be submitted to FDA this year.

Sofpironium bromide is a structural analog of glycopyrrolate; sofpironium bromide was retro metabolically designed. This process entails the identification of a known inactive metabolite of an active drug. The metabolite is then modified to an active form that will undergo a predictable, one-step transformation back into the inactive metabolite in vivo. Sofpironium, once applied, is metabolized to glycopyrrolate.

In the US Phase 3 clinical trials (Cardigan I and Cardigan II), sofpironium bromide gel, 15% met all primary and secondary endpoints with statistical significance and was generally well tolerated.

Each of the multicenter, randomized, double-blinded, vehicle-controlled Cardigan studies enrolled approximately 350 subjects nine years of age and older with primary axillary hyperhidrosis. Subjects applied sofpironium bromide gel, 15% or placebo to their underarms once daily at bedtime for six consecutive weeks with a two-week post-treatment follow-up. The primary endpoint was the proportion of subjects achieving at least a 2-point improvement in Hyperhidrosis Disease Severity Measure–Axillary (HDSM-Ax) score from baseline. Results showed 49.3 percent and 63.9 percent of subjects receiving active treatment met the primary endpoint, compared to 29.4 percent and 47 percent of controls, respectively.

Hyperhidrosis by the Numbers

4.8% Estimated prevalence in the US

15.3 million People with hyperhidrosis in the US

70% Report severe excessive sweating in at least one body area

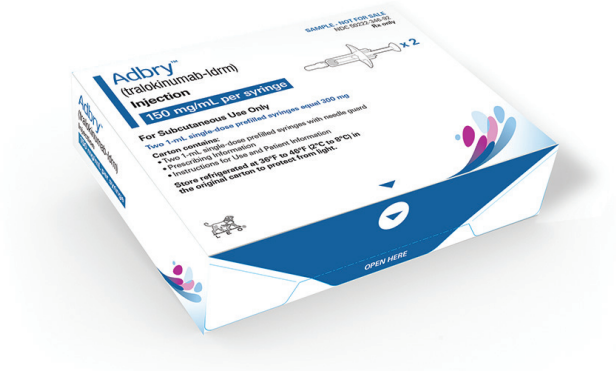
51% Have discussed their excessive sweating with a health care professional

—Arch Dermatol Res. 2016; 308(10): 743–749.

Treatment-Emergent Adverse Events (TEAEs) were mild or moderate in severity and transient. Common adverse events (incidence ≥2 percent) observed in the sofpironium bromide treatment group were dry mouth (11.6 percent, 17.2 percent), blurred vision (5.2 percent, 11.7 percent), application site pain (6.4 percent, 10 percent), application site erythema (5.2 percent, 7.8 percent), mydriasis (7.5 percent, five percent), application site pruritus (6.4 percent, 2.2 percent), application site dermatitis (5.8 percent, 5.6 percent), urinary retention (1.2 percent, 3.3 percent), application site irritation (1.2 percent, 3.3 percent), dry eye (0.6 percent, 3.3 percent), headache (1.2 percent, 2.2 percent), constipation (0.6 percent, 2.2 percent) and urinary hesitation (0.6 percent, 2.2 percent), respectively. Five (2.9 percent) and nine (five percent) active treatment subjects discontinued the Cardigan I and II studies, respectively, due to a TEAE. No treatment-related Serious Adverse Events (SAEs) were reported.

Kaken Pharmaceutical Co., Ltd., Brickell's development partner on sofpironium bromide, launched Ecclock for the once-daily treatment of primary axillary hyperhidrosis in Japan in November 2020, marking the first commercialization of sofpironium bromide for any indication worldwide.

Tralokinumab



Approved late last year, Adbry (tralokinumab-ldrm) from LEO Pharma Inc. is the first FDA approved biologic that specifically binds to and inhibits the IL-13 cytokine. It is indicated for the treatment of moderate to severe atopic dermatitis in adults 18 years or older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

IL-13 has been shown to be more strongly associated with the inflammation of atopic dermatitis than psoriasis.

> "PAD technology allows for the suspension of oil in water without significant use of surfactants to help stabilize the emulsion. The intention is to maximize the known therapeutic benefit of the Calcipotriene/BDP combination while optimizing the topical treatment experience with a non-greasy, moisturizing, rapidly-absorbing cream."

The ECZTRA 1, 2 and ECZTRA 3 pivotal Phase 3 trials included nearly 2,000 adult patients with moderate to severe atopic dermatitis. In all three pivotal trials, Adbry 300mg every other week alone or with topical corticosteroids (TCS) as needed met the primary endpoints at Week 16 as measured by an Investigator Global Assessment score of clear or almost clear skin (IGA 0/1) and/or at least a 75% improvement in the Eczema Area and Severity Index score (EASI-75), and the secondary endpoint of reduction of weekly average Worst Daily Pruritus NRS of ≥ 4 points on the 11-point itch NRS.

In clinical trials, the safety of Adbry was well established. The overall frequency of adverse events was comparable for active treatment compared to placebo. The most common adverse events (incidence ≥1% and greater than placebo) were upper respiratory tract infections, conjunctivitis, injection site reactions, and eosinophilia.

Adbry will be available in a 150mg/mL prefilled syringe for subcutaneous injection. The initial dose is 600mg followed by 300mg every other week. For patients weighing less than 100kg who achieve clear or almost clear skin at week 16, a dosage of 300mg every four weeks may be considered.

Calcipotriene/BDP Cream

Fixed dose combination calcipotriene and betamethasone dipropionate (Calcipotriene/BDP) is among the most commonly-prescribed topical interventions for management of psoriasis. MC2 therapeutics has developed a stable cream formulation of Calcipotriene/BDP (Wynzora) using PAD Technology. EPI Health is partnering on marketing/distribution. PAD technology allows for the suspension of oil in water without significant use of surfactants to help stabilize the emulsion. The intention is to maximize the known therapeutic benefit of the Calcipotriene/BDP combination while optimizing the topical treatment experience with a non-greasy, moisturizing, rapidly-absorbing cream.

The JAKs are Here

The approval of Opzelura topical cream (ruxolitinib, Incyte) late last year for management of atopic dermatitis officially marked the start of the JAK era in dermatology. Last month brought the approvals of oral Cibinqo (abrocitinib, Pfizer) and Rinvoq (upadacitinib, AbbVie), also for atopic dermatitis.

So what are the JAKs and how do they work?

Janus Kinases are key drivers of cytokine signaling and inflammatory response. More specifically, the JAK/STAT (signal transducer and activator of transcription proteins) pathway is operative in inflammatory disease. When cytokines bind to cell-surface receptors, JAKs are activated and phosphorylate the receptor. This facilitates the binding of STAT proteins to the phosphates. JAKs then phosphorylate the STATs to form a dimer that is able to enter the nucleus and bind to DNA. Subsequently, targeted gene transcription results in the expression of additional cytokines.[1]

There are a number of JAKs with differing affinities. JAK 1/JAK 3 pathways appear to impact Th2 pathways, such as for atopic dermatitis, while JAK 2/TYK 2 pathways are associated with psoriasis. In addition, JAK inhibitors are being investigated for use in vitiligo and alopecia areata.

For more on recently approved Opzelura and investigational deucravacitinib, read on here. For more on abroctinib and upadacitinib, see the pages 43 and 46.

Opzelura cream 1.5% is approved for the short-term and non-continuous chronic treatment of mild to moderate AD in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies, or when those therapies are not advisable.

Research shows dysregulation of the JAK-STAT pathway contributes to key features of AD such as itch, inflammation and skin barrier dysfunction.

FDA approval was based on data from the TRuE-AD (Topical Ruxolitinib Evaluation in Atopic Dermatitis) clinical trial program, which consisted of two randomized, double-blind, vehicle-controlled Phase 3 studies (TRuE-AD1 and TRuE-AD 2) involving more than 1,200 adolescents and adults with mild to moderate AD.

In the studies, 53.8 of active treatment subjects in TRuE-AD1 and 51.3 percent in TRuE-AD2 achieved IGA Treatment Success (IGA-TS, primary endpoint) at Week 8 (defined as an IGA score of 0 [clear] or 1 [almost clear] with at least a 2-point improvement from baseline), compared to 15.1% for vehicle in TRuE-AD1 and 7.6 percent in TRuE-AD2.

Active treatment with ruxolitinib was associated with a clinically meaningful reduction in itch from baseline at Week 8, as measured by a ≥4-point reduction in the itch Numerical Rating Scale (itch NRS4). Approximately half of treated subjects (52.2 percent in TRuE-AD1 and 50.7 percent in TRuE-AD2) achieved this endpoint. Rates were significantly lower for vehicle (15.4% in TRuE-AD1, 16.3% in TRuE-AD2).

Deucravacitinib inhibits Tyrosine Kinase 2 (Tyk2). It is in development by Bristol Myers Squibb for the treatment of psoriasis. In the POETYK PSO-1 and POETYK PSO-2 trials, deucravacitinib 6mg once daily met both co-primary endpoints versus placebo; significantly more patients achieved PASI 75 response and a static Physician's Global Assessment (sPGA) score of clear or almost clear after 16 weeks of treatment.

The studies compared deucravacitinib against placebo and against apremilast, which the Tyk2 inhibitor achieving greater skin clearance than the oral PDE4 inhibitor. At Week 16, 58.7 percent and 53.6 percent of patients receiving deucravacitinib achieved PASI 75 response, respectively, versus 12.7 percent and 9.4 percent, respectively, of those receiving placebo and 35.1 percent and 40.2 percent, respectively, of those receiving apremilast.

At Week 24, rates of PASI 75 response were 69 percent and 59.3 percent for patients receiving deucravacitinib, versus 38.1 percent and 37.8 percent for apremilast.

At Week 16, roughly half of subjects receiving deucravacitinib had sPGA 0/1 response: 53.6 percent and 50.3 percent, respectively. Rates of sPGA 0/1 response for placebo were 7.2 percent and 8.6 percent, respectively and for apremilast were 32.1 percent and 34.3 percent for apremilast. By Week 24, rates of sPGA 0/1 response reached 58.4 percent and 50.4 percent for deucravacitinib respectively, versus 31.0 percent and 29.5 percent for apremilast.

Deucravacitinib provided better results in scalp psoriasis compared to apremilast or placebo. At week 16, 70.8 percent and 60.3 percent, respectively, of deucravacitinib-treated patients achieved scalp sPGA0/1. This compares to rates of 17.4 percent and 17.3 percent for placebo and 39.1 percent and 37.3 percent for apremilast.

1. Damsky W, King BA. JAK inhibitors in dermatology: The promise of a new drug class. J Am Acad Dermatol. 2017 Apr;76(4):736-744.

> "PDE$_4$ has been shown to be expressed in keratinocytes and fibroblasts. cAMP-PDE activity in leukocytes is significantly elevated in patients with AD compared to healthy controls. Regulation of PDE$_4$ is expected to reduce cytokine activation and subsequent inflammation."

In a Phase 3 study comparing MC2-01 Cream to Calcipotriene/BDP topical suspension, MC2-01 demonstrated non-inferiority to comparator at week 8 in terms of the primary end-point: treatment success defined as a minimum two-point decrease in the Physician Global Assessment (PGA) score.

In terms of percentage reduction in PASI from baseline to Week 8, MC2-01 outperformed the Calcipotriene/BDP topical suspension: 64.8 percent versus 52.3 percent. Patients statistically significantly rated MC2-01 cream superior to Calcipotriene/BDP topical suspension in terms of treatment convenience.

The adverse events seen in the trial were described as predictable pharmacological class effects typically associated with calcipotriene and topical corticosteroids, and the safety profile of the combination was similar for both study formulations.

Roflumilast

PDE$_4$ is shown to increase cAMP conversion to AMP and increase cytokine production. As such, increased PDE$_4$ results in immune activation and overexpression of several Th2 cytokines (IL-4, IL-5, and IL-13); Th1 cytokines, TNF-alpha, IL-12; and Th22 cytokine IL-22. There is also activation of the Th17 pathway. PDE$_4$ has been shown to be expressed in keratinocytes and fibroblasts. cAMP-PDE activity in leukocytes is significantly elevated in patients with AD compared to healthy controls. Regulation of PDE$_4$ is expected to reduce cytokine activation and subsequent inflammation.

Roflumilast is a topical PDE$_4$ inhibitor under development (Arcutis Biotherapeutics) for multiple dermatologic indications, including AD, psoriasis, seborrheic dermatitis, and vitiligo. Cream, foam, and lotion formulations are all in development.

DERMIS-1 and DERMIS-2 are identical Phase 3 studies evaluating topical roflumilast cream (ARQ-151) once daily for chronic plaque psoriasis. In the trials, significantly more patients treated with roflumilast cream 0.3 percent reached IGA success—defined as clear or almost clear with at least a 2-grade improvement from baseline—compared to vehicle-treated patients (42.4 percent and 37.5 percent vs. 6.1 percent and 6.9 percent, respectively).

A secondary endpoint in the studies was IGA success in the intertriginous areas (I-IGA). Roflumilast demonstrated statistically significant improvements over vehicle (clear or almost clear with at least a 2-grade improvement from baseline). Across both trials, approximately 40 percent of patients achieved a 75 percent reduction in PASI scores (PASI-75) by week eight.

Roflumilast safety and tolerability were similar to that for vehicle, including pooled rates for TEAEs (3.9 percent roflumilast vs. 3.6 percent vehicle), any AE leading to discontinuation (one percent roflumilast vs 1.3 percent vehicle) and application site pain (one percent roflumilast vs 0.3 percent vehicle). There were no treatment-related serious AEs, and local tolerability was highly favorable for roflumilast as reported by patient and investigator assessment of irritation, burning, and stinging.

Tapinarof

Tapinarof 1% cream (Dermavant) is a therapeutic aryl hydrocarbon receptor (AhR)-modulating agent under FDA review for the treatment of psoriasis and being investigated for AD. The bound AhR-ARNTcomplex binds to DNA and modulates gene expression. By modulating the AhR, tapinarof forms a ligand with the AhR-ARNT complex; the ligand complex translocates and is thought to modify gene expression, leading to specific effects in the skin. These effects include a reduction in the expression of Th17 cytokines and associated decrease in inflammation in psoriasis; a reduction in Th2 cytokines and associated decrease of inflammation in atopic dermatitis; an increase in antioxidant activity via the Nrf2 pathway and associated decreased in oxidative stress; and an increase in filaggrin, loricrin, and involucrin with associated normalization of skin barrier function.

The Phase 3 program for topical tapinarof includes three trials of adults with plaque psoriasis: PSOARING 1 and PSOARING 2, the pivotal efficacy trials, and PSOARING 3, a long-term, open-label safety study. The primary endpoint in PSOARING 1 and PSOARING 2 was the percentage of patients achieving a PGA score of clear (0) or almost clear (1) with a minimum 2-grade improvement from baseline, compared with vehicle at week 12.

Results showed that 35.4 percent and 36.1 percent of treated patients met the endpoint, compared to six percent and 6.3 percent of controls, respectively. In all, up to 80 percent of patients had at least a one-grade improvement in PGA.

DID YOU KNOW?

Pfizer, Inc. is set to acquire Arena Pharmaceuticals, Inc., having entered into a definitive agreement late last year. Under terms of the agreement, Pfizer will acquire all the outstanding shares of Arena for $100 per share in an all-cash transaction for a total equity value of approximately $6.7 billion. The boards of directors of both companies have unanimously approved the transaction.

Arena's portfolio includes therapeutic candidates in gastroenterology, dermatology, and cardiology, including etrasimod.

Thirty-six percent and 47.6 percent of treated subjects achieved PASI 75 at week 12, the secondary endpoint, compared to 10.2 percent and 6.9 percent of controls, respectively.

Reported results of an interim analysis of data from PSOARING 3 shows that 57.3 of subjects who entered the study with a PGA score ≥ 2 achieved a PGA score of 0 or 1, and 39.2 of subjects included in the interim analysis achieved complete disease clearance (PGA score = 0). There was no evidence of tachyphylaxis.

Tapinarof cream, 1% was well-tolerated; the discontinuation rate due to adverse events (AEs) at the time of the interim analysis was 5.8, generally consistent with the PSOARING 1 (5.6) and PSOARING 2 (5.8) pivotal trials. No new safety signals were observed.

The majority of AEs were localized to site of application, and mild to moderate in nature. The most commonly reported AEs were folliculitis, contact dermatitis, and upper respiratory tract infection.

In studies of atopic dermatitis, 46 of subjects receiving tapinarof achieved clear or almost clear and ≥2-grade improvement after 12 weeks vs. 28 on vehicle. In fact, active treatment with tapinarof demonstrated statistical significance over vehicle after four weeks of treatment and at multiple time points thereafter.

Spesolimab

Spesolimab is a novel, humanized, selective antibody that blocks the activation of the interleukin-36 receptor (IL-36R), a signaling pathway within the immune system shown to be involved in several autoimmune diseases pathogeneses, including generalized pustular psoriasis (GPP). Boehringer Ingelheim is developing the biologic therapy.

Results of the pivotal Phase 2 Effisayil 1 trial, showed spesolimab significantly improved signs and symptoms of GPP in patients experiencing a flare. In the 12-week trial, 53 patients experiencing a GPP flare were treated with a single 900mg intravenous dose of spesolimab or placebo. At one week, 54 percent of patients treated with spesolimab showed no visible pustules, compared to six percent of those treated with placebo. Pustular and skin clearance continued for the duration of the study. At the end of the study period, 43 percent of patients treated with spesolimab showed clear/almost clear skin, compared to 11 of those in the placebo group.

Non-serious infections rates were higher in the spesolimab group compared with placebo during the course of the study; no pattern was identified regarding pathogen and affected organs. Two patients reported drug reactions with eosinophilia and systemic symptoms.

Now underway, the Effisayil-2 trial is designed to investigate spesolimab as a maintenance treatment to prevent the occurrence of GPP flares. The Effisayil-ON trial is an open label five-year extension study.

Ligelizumab

Ligelizumab (Novartis), a next generation monoclonal anti-immunoglobulin E (IgE) antibody, has been granted Breakthrough Therapy designation for the treatment of chronic spontaneous urticaria (CSU), also known as chronic idiopathic urticaria (CIU), in patients who have an inadequate response to H1-antihistamine treatment.

Ligelizumab is thought to work by blocking the IgE/FcεRI pathway, a key driver of the inflammatory process in CSU. In a Phase 2b dose-finding trial, more patients experienced complete resolution of wheals (hives) with ligelizumab compared with omalizumab, and no safety concerns were found with ligelizumab compared with omalizumab or placebo.

Recently reported top-line results from the PEARL 1 and PEARL 2 Phase 3 studies in CSU, show that ligelizumab met its primary endpoint of superiority versus placebo at Week 12, but not versus omalizumab.

Etrasimod

Etrasimod (Arena Pharmaceuticals) is an investigational selective S1P receptor modulator for once daily, oral

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GPP by the Numbers

64% Proportion of dermatologists who cited steroid withdrawal as a primary trigger for GPP. It was followed by infection (58%) and stress (50%)

38% Proportion of dermatologists who said it was at least "somewhat common" for a flare to require hospitalization.

72% Dermatologists who say treatments are too slow to control GPP flares.

—Dermatol Ther (Heidelb). 2021 Apr;11(2):529-541.

administration. It is designed to partially and reversibly reduce lymphocyte levels at sites of inflammation, while maintaining components of immune function. It is under investigation for a range of diseases, including atopic dermatitis and alopecia areata.

In the Phase 2b ADVISE trial, 140 individuals with chronic, moderate to severe eczema present for at least a year were randomized into three equal cohorts to receive etrasimod 1mg, etrasimod 2mg, or placebo, once daily for 12 weeks. At 12 weeks, 29.8 percent of subjects in the etrasimod 2mg group had reductions of clinician-reported vIGA of 0 or 1 (representing "clear" or "almost clear" skin, and improved by at least 2 points), compared to 13 percent for placebo.

Individuals in the etrasimod 2mg cohort had a statistically significant improvement in itch, as demonstrated by percent change from baseline in the peak pruritus numeric rating scale (PP-NRS), as early as Week 2, compared to placebo.

Etrasimod was generally well-tolerated in ADVISE; there were no serious adverse events or opportunistic or serious infections observed. Nausea, constipation, back pain, and dizziness were the most common adverse events occurring for >5% of treated patients and greater than placebo. ■