Approvals in Psoriasis and Skin Cancer Highlight a Year of Innovation in Skin Disease Management

After periods of low drug approval rates, the last year brought several new agents to market.

**ACNE AND ROSACEA**

FDA approval of Finacea® (azelaic acid) Foam, 15% for the topical treatment of the inflammatory papules and pustules of mild to moderate rosacea was based on results from two pivotal clinical trials comparing Finacea® Foam to its foam vehicle. Treatment with Finacea® Foam resulted in a higher Investigator’s Global Assessment (IGA) success rate compared to vehicle (32.1% vs. 23.4% in Trial 1 and 43.4% vs. 32.5% in Trial 2), as well as a greater reduction in the mean nominal change of inflammatory lesion count from baseline to the end of the 12-week treatment period (-13.2 vs. -10.3 in trial 1 and -13.3 vs. -9.5 in trial 2).

Galderma’s Epiduo® Forte (adapalene and benzoyl peroxide) Gel, 0.3%/2.5%, for the once-daily, topical treatment of acne vulgaris is the first combination of these strengths adapalene, and benzoyl peroxide developed for the moderate to severe acne population. FDA approval of Epiduo Forte Gel was based on a pivotal phase 3, multicenter, randomized, double-blind, 12-week, vehicle-controlled study in which it met each of its primary efficacy endpoints when compared to vehicle gel in 217 acne patients. The study demonstrated superiority of Epiduo Forte Gel over vehicle gel in the overall study population (moderate to severe) at week 12 for the Investigator’s Global Assessment Success Rate and for changes in inflammatory and non-inflammatory lesion count. Additionally, subjects who were “severe” at baseline (50 percent) were required to go from “severe” to “clear” or “almost clear” within the 12-week trial to be considered a treatment success. More than half of study subjects treated with Epiduo Forte Gel reported a marked improvement in their severe acne (50.5 percent).

In the clinical trial, Epiduo Forte Gel was shown to be safe and well tolerated, and most adverse events (AEs) were mild to moderate in severity. The most commonly reported adverse events (≥1%) in patients treated with Epiduo Forte Gel were skin irritation, eczema, atopic dermatitis, and skin burning sensation.

**PSORIASIS**

Cosentyx™ (secukinumab) from Novartis became the first IL-17 receptor inhibitor approved for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Results from 10 phase 2 and 3 studies, including over 3,990 patients with moderate-to-severe plaque psoriasis, demonstrate that Cosentyx resulted in clear or almost clear skin in the majority of patients and had an acceptable safety profile.

The phase 3 clinical program included four placebo-controlled studies, that examined Cosentyx 300mg and 150mg in patients with moderate-to-severe plaque psoriasis. In these studies, Cosentyx met all primary and key secondary endpoints, including Psoriasis Area and Severity Index (PASI) 75 and 90 and Investigator’s Global Assessment modified 2011 (IGA) 0/1 responses, showing significant skin clearance at Week 12.

Findings from the phase 3 AMAGINE-3 trial suggest that the investigational IL-17 inhibitor brodalumab may be superior to ustekinumab in treating patients with moderate to severe psoriasis. Investigators evaluated more than 1,800 patients who were randomized to receive brodalumab 210mg, brodalumab 140mg, ustekinumab, or placebo. They found that 37 percent of patients receiving a 210mg dosage...
The FDA granted 510(k) clearance to Oculus Innovative Sciences, Inc. for Alevicyn SG Antipruritic Spray Gel with both prescription and over-the-counter indications. The Alevicyn SG prescription product, using Microcyn® Technology, is indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including radiation dermatitis and atopic dermatitis. It may also be used to relieve the pain of first- and second-degree burns and helps to relieve dry waxy skin by maintaining a moist wound and skin environment.

Under the terms of the agreement, Valeant will make an up-front payment to AstraZeneca of $100 million as well as additional pre-launch milestones of up to $170 million and further sales related milestone payments of up to $175 million following launch. After approval, AstraZeneca and Valeant will share profits.

On the topical treatment front, the FDA approved LEO Pharma’s Enstilar Foam, an alcohol-free foam formulation in a pressurized spray, for the topical treatment of plaque psoriasis in adults 18 years of age and older. In the phase 3 clinical trial, more than half of patients treated with Enstilar were “Clear” or “Almost Clear” by week four as assessed by the Investigator Global Assessment (IGA) score of disease severity. Additionally, more than half of patients treated with Enstilar achieved a 75 percent improvement in Psoriasis Area and Severity Index (PASI) score from baseline. Adverse reactions were reported in less than one percent of patients treated with Enstilar and included application site irritation, application site pruritus, folliculitis, skin hypopigmentation, hypercalcemia, urticaria, and exacerbation of psoriasis.

Although most Americans eat enough, they may not eat the right things. For any patient with alopecia, check levels and recommend specific dietary changes or supplements as needed, says Melissa Piliang, MD. For every patient, recommend at least a multivitamin to cover the gaps that will develop in all diets.

Dr. Piliang also highlights the need to reassure patients about hair loss and the ability to manage it: "I think it’s really important to approach them in a caring manner and not in a dismissive manner. So many patients come to me who’ve seen several other dermatologists who’ve been told, “You’re fine. There’s nothing wrong. Look, you have enough hair. You’re fine. And that just ramps up their anxiety level.” The more you can listen to their concerns and answer their questions and reassure them, then the better the whole experience will be.”

Learn more: http://dermtube.com/series/ask-an-expert/assessing-and-managing-alopecia/
HIDRADENITIS SUPPURATIVA

With FDA approval this summer, AbbVie’s Humira® (adalimumab) is now the first and only FDA-approved therapy for the treatment of moderate to severe hidradenitis suppurativa (HS) in adults. FDA previously had granted Humira orphan drug designation for the treatment of moderate to severe HS (Hurley Stage II and Hurley Stage III disease), a population of fewer than 200,000 patients. Orphan drug designation provides the potential to be granted seven years of market exclusivity for the treatment of moderate to severe HS.

FDA approval was based on results of two phase 3 studies, PIONEER I and PIONEER II, that included 633 people with moderate to severe HS. Patients in these studies were randomly assigned to receive either Humira or placebo in addition to daily use of topical antiseptic. Both studies showed that more patients given Humira had reductions in the total number of abscesses and inflammatory nodules than patients given placebo. No new safety risks were identified in these trials.

SKIN CANCER

The FDA granted regular approval for the combination of Tafinlar® (dabrafenib) plus Mekinist® (trametinib) from Novartis for the treatment of patients with BRAF V600E/K mutation-positive unresectable or metastatic melanoma as detected by an FDA-approved test. This is the first targeted therapy combination demonstrating more than two years overall survival in such patients.

More than 5,000 patients have had experience with the combination use of Tafinlar plus Mekinist in clinical trials and since its initial approval in 2014, the combination of Tafinlar plus Mekinist has extended the lives of many patients with BRAF mutation-positive metastatic melanoma. Regular approval was based on survival data from two Phase III studies: COMBI-d and COMBI-v in which Tafinlar plus Mekinist demonstrated statistically significant progression-free survival (PFS) and overall survival (OS) compared with dabrafenib or vemurafenib, in patients with BRAF V600E/K mutation-positive unresectable or metastatic melanoma.

FDA also approved Cotellic (cobimetinib) to be used in combination with Zelboraf (vemurafenib) to treat advanced melanoma that has spread to other parts of the body or can’t be removed by surgery, and that has a BRAF V600E or V600K mutation.

Cotellic is a MEK inhibitor. Vemurafenib is a BRAF inhibitor that affects a different part of the same pathway and was approved in 2011 to treat patients with melanoma that has spread to other parts of the body or cannot be removed by surgery, whose tumors express a gene mutation called BRAF V600E, as detected by an FDA approved test. Health care providers should confirm the presence of BRAF V600 E or V600K mutation in their patients’ tumor specimens using one of the available FDA approved tests prior to starting patients on treatment with Cotellic in combination with vemurafenib.

The safety and efficacy of Cotellic taken in combination with vemurafenib were demonstrated in a randomized clinical study of 495 patients with previously untreated, BRAF V600 mutation-positive melanoma that is advanced or cannot be removed by surgery. All study participants received vemurafenib and were then randomly selected to also take either Cotellic or a placebo. On average, patients taking Cotellic plus vemurafenib experienced a delay in the amount of time it took for their disease to worsen (approximately 12.3 months after starting treatment) compared to approximately 7.2 months after starting treatment for those taking vemurafenib only. In addition, patients taking Cotellic plus vemurafenib lived longer, with approximately 65 percent of patients alive 17 months after starting treatment as compared to half of those taking vemurafenib only. Additionally, 70 percent of those taking Cotellic plus vemurafenib experienced complete or partial shrinkage of their tumors, compared to 50 percent among those taking vemurafenib plus placebo.

The most common side effects of treatment with Cotellic in combination with vemurafenib are diarrhea, photosensitivity reaction, nausea, fever (pyrexia) and vomiting.

FDA approved Bristol-Myers Squibb Company’s Yervoy (ipilimumab) 10mg/kg for the adjuvant treatment of
patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1mm who have undergone complete resection including total lymphadenectomy. Approval is based on clinical data from a pivotal Phase 3 trial, CA184-029 (EORTC 18071), which demonstrated Yervoy 10mg/kg significantly improved recurrence-free survival (RFS) vs. placebo in this setting, with a 25 percent reduction in the risk of recurrence or death. The median RFS was 26 months (95% CI: 19, 39) for Yervoy vs. 17 months (95% CI: 13, 22) for placebo (hazard ratio [HR]=0.75; 95% CI: 0.64, 0.90; p<0.002). Yervoy is the first and only FDA-approved immune checkpoint inhibitor in the adjuvant treatment for fully resected Stage III melanoma (lymph node >1 mm).

Yervoy is associated with a Boxed Warning and can result in severe to fatal immune-mediated adverse reactions.

The phase 3 trial, CA184-029 (EORTC 18071), is a cooperative group study initiated in 2008 by the European Organization for Research and Treatment of Cancer (EORTC) evaluating the 10 mg/kg dose in the adjuvant setting. With the goal of advancing treatment options for the adjuvant treatment of melanoma, Bristol-Myers Squibb is working with the Eastern Cooperative Oncology Group (ECOG) and is conducting an ongoing study to investigate other dosing options for Yervoy in the adjuvant setting.

The Biologics License Application for Amgen’s Imlygic™ (talimogene laherparepvec) received FDA approval for the local treatment of unresectable cutaneous, subcutaneous and nodal lesions in patients with melanoma recurrent after initial surgery. Imlygic has not been shown to improve overall survival or have an effect on visceral metastases. Imlygic is the first oncolytic viral therapy approved by the FDA.

Imlygic is a genetically modified herpes simplex virus type 1 designed to replicate within tumors and produce the immunostimulatory protein granulocyte-macrophage colony-stimulating factor (GM-CSF). Imlygic causes cell lysis, which ruptures tumors, releasing tumor-derived antigens, which along with GM-CSF, may promote an anti-tumor immune response. However, the exact mechanism of action is unknown.

Amgen anticipates the average cost of Imlygic therapy to be approximately $65,000. Given that Imlygic represents a novel and first-in-class oncolytic viral therapy, Amgen expects variability of Imlygic dosing from patient to patient and intends to work with the healthcare community to implement a program that helps limit the average cost of Imlygic therapy to $65,000 for eligible participating institutions.

The FDA granted accelerated approval to nivolumab (Opdivo Injection, Bristol-Myers Squibb Company) in combination with ipilimumab for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma. In a clinical trial that randomized (2:1) 142 patients to receive nivolumab plus ipilimumab (n=95) or ipilimumab plus placebo (n=47), there was a significant improvement in ORR for combination treatment. The ORR was 60% in the nivolumab plus ipilimumab group (n=72) and 11% in the ipilimumab group (n=37), an improvement in ORR of 49%. Among the 140 patients with BRAF V600 wild-type or mutation-positive melanoma who received at least one dose of nivolumab or ipilimumab, serious adverse reactions (62% vs. 39%), adverse reactions leading to permanent discontinuation (43% vs. 11%) or dose delay (47% vs. 22%), and grade 3 or 4 adverse reactions (69% vs. 43%) all occurred more frequently in patients receiving the combination (n= 94) compared with those receiving single-agent ipilimumab (n=46).

Following reports of severe allergic reactions and herpes zoster (shingles) associated with the use of Picato gel (ingenol mebutate), FDA has ordered labeling changes for the drug. The agency has also received reports of severe eye injuries and skin reactions associated with the application of Picato gel, which is approved for the treatments of actinic keratoses. Some cases were associated with the product not being used according to the instructions for use on the label. The label changes will warn about these new safety risks and provide additional instructions on the safe and appropriate application of the product.

An ongoing controversy over certification of Mohs micrographic surgeons may be no closer to a resolution, but Chief Cosmetic Surgery Editor for Practical Dermtology® magazine, Joel Schlessinger, MD, FAAD, is calling for dialogue. He spoke with DermTube.com about the issue.

Watch now to learn more: http://dermtube.com/video/mohs-certification-finding-a-middle-ground/