New Drug Update: Eucrisa (crisaborole) for eczema (atopic dermatitis)

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Introduction:

Eczema is a chronic inflammatory skin disease that affects nearly 18 million children and adults in the United States. Approximately 90% of the patients have mild to moderate symptoms.[6,7] It is the most common atopic dermatitis (AD) skin disease, and it typically begins in childhood and lasts potentially throughout adulthood. The cause is unknown but believed to be a combination of genetic, immune and environmental factors.[6,7] Symptoms may include red, swollen, scaly and crusted bumps that can be extremely itchy. Scratching can worsen symptoms and can lead to swelling, cracking, and "weeping" clear fluid, which can coarsen and thicken the skin.[6,7,9,10] AD is associated with multiple comorbidities, and has deleterious impacts on both individual and family quality of life. Some comorbidities include sleep impairment, asthma, allergic rhinitis, food allergies, and various cutaneous infections.[4] Over the past 15 years, no significant advances have been made in the treatment of atopic dermatitis. However, crisaborole has the potential to be an important first-line treatment option. [6]

Crisaborole is an anti-inflammatory phosphodiesterase (PDE-4) inhibitor that was approved by the U.S. Food and Drug Administration (FDA) on December 14, 2016. Crisaborole is marketed and produced by Pfizer Inc. as Eucrisa for the treatment of mild to moderate eczema in patients two years of age and older.[9,10] Crisaborole is the first and only non-steroidal topical monotherapy that inhibits the PDE-4 enzyme in the skin. Although the specific mechanism by which crisaborole exerts its therapeutic action is not well defined, it is believed to target and inhibit PDE-4.[9] Overactive PDE-4 has been shown to contribute to the signs and symptoms of atopic dermatitis.[7] Crisaborole results in increased intracellular cyclic adenosine monophosphate (cAMP) levels.

Clinical Pharmacology (Pharmacodynamics and Pharmacokinetics):[4,5,11]

Pharmacodynamics:

At therapeutic doses, crisaborole is not expected to prolong QTc to any clinically relevant extent.

Pharmacokinetics:

Systemic concentrations of crisaborole were at steady state by day 8. On day 8, the maximum plasma concentration (C_{max}) was 127 ± 196ng/mL, and the area under the concentration curve from 0 to 12 hours post dose (AUC_{0-12}) was 949 ± 1240ng-h/mL. Based on the ratios of AUC_{0-12} between Day 8 and Day 1, the mean accumulation factor for crisaborole was 1.9. Crisaborole is substantially metabolized into two inactive metabolites, 5-(4-cyanophenoxy)-2-hydroxyl benzylalcohol (metabolite 1) and 5-(4-cyanophenoxy)-2-hydroxyl benzoic acid (metabolite 2). In vitro studies using human liver microsomes indicated that crisaborole and metabolite 1 are not expected to inhibit cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4. Studies for metabolite 2 showed that it did not inhibit activities of CYP2C19, 2D6, and 3A4. However, it was a weak inhibitor for CYP1A2 and 2B6. The most sensitive enzyme, CYP2C9 was further investigated using warfarin as a CYP2C9 substrate. The results showed no drug interaction. Also, crisaborole and metabolites 1 and 2 are not expected to induce CYP enzymes.[11] Ninety-seven percent of crisaborole that is absorbed through the skin is bound to human plasma proteins; it is metabolized into an inactive metabolite that is eliminated by the kidneys.

Clinical Trial: [1,7,9,10,11]

FDA approval was based on a clinical development program that included two large, identical, multicenter, randomized, double-blinded, parallel-group, vehicle-controlled (non-medicated ointment) phase 3 trials (Trial 1 and Trial 2) conducted in the United States. The studies included 1,522 patients between the ages of 2 and 79 with mild to moderate atopic dermatitis affecting at least 5% of the body surface area (BSA). The Investigator's Static Global Assessment (ISGA) was used to assess erythema (redness), induration (hardening), papulation (formation of papules), oozing, and crusting on a scale of 0 to 4. At baseline, 38.5% of the subjects had a score of 2 (mild) and 61.5% had a score of 3 (moderate). The use of topical or systemic corticosteroids or topical calcineurin inhibitors was prohibited during the study. Subjects who were on stable regimens of oral antihistamines or inhaled corticosteroids could continue these treatments.[4] In both trials, subjects were randomized 2:1 to receive crisaborole or vehicle. Crisaborole or vehicle was applied to affected skin twice daily for 28 consecutive days. The primary endpoint at day 29 was defined as the proportion of patients achieving an ISGA score of 0 (clear) or 1 (almost clear), with at least a 2-grade improvement from baseline. Crisaborole was an effective treatment that achieved statistically significant results compared to the vehicle for the primary endpoint in adults and children 2 years and older (Trial 1- 32.8% *versus* 25.4%, p=0.038; Trial 2 – 31.4% *versus* 18.0%, p <0.001). In both trials, crisaborole was statistically superior ($p < 0.05$) to placebo for the primary endpoint, and also for the secondary endpoint ISGA 0 or 1.[5]

Efficacy results were seen in some patients as early as day 8 (first post-baseline assessment) with 13.4% of crisaborole patients achieving success in ISGA *versus* 4.5% with vehicle in Trial 1and 15.9% crisaborole *versus* 6.3% vehicle in Trial 2. The only adverse reaction

reported by more than 1% of patients receiving crisaborole was pain at the application site, such as stinging or burning (4%, n = 45) versus vehicle (1%, n = 6). The rate of study discontinuation due to adverse reactions was the same for both the crisaborole group and vehicle (1.2%). Crisaborole was more effective in females and Caucasians, but there were no age differences observed (limited numbers patients over the age of 65 precluded analysis in this group). Efficacy between the two trials among gender, race, and age is summarized in Table 1.

Table 1: Summary baseline demographics for the intent-to-treat (ITT) population[7]

	Trial 1:		OR*	Trial 2:		OR
	Crisaborole (n=503)	Vehicle (n=256)		Crisaborole (n=513)	Vehicle (n=250)	
Gender						
Female	32.50%	24.20%	1.5	29.00%	14.8	2.35
Male	33.20%	26.90%	1.35	34.40%	22.10%	1.85
Age						
2-6	33.60%	32.10%	1.07	27.40%	12.40%	2.67
7-11	31.40%	25.40%	1.34	42.90%	20.10%	2.99
12-17	34.20%	19.20%	2.19	26.30%	19.70%	1.46
18+	31.60%	22.70%	1.58	28.10%	27.70%	1.02
Race						
Caucasians	33.80%	25.20%	1.52	33.10%	18.80%	2.14
Black	34.50%	32.70%	1.08	29.70%	17.70%	1.96
Others	23.20%	12.90%	2.09	26.30%	14.90%	2.05

*OR - Odds Ratio

Crisaborole is available as a topical ointment – it is not intended to be ingested or for ophthalmic, oral, or vaginal administration. It should be applied as a thin layer twice daily to affected areas of skin. Crisaborole is contraindicated in patients with known hypersensitivity to crisaborole or any component of the formulation. Warnings and precautions include

hypersensitivity reactions, including contact urticarial (hives) and should be suspected in the event of severe pruritus, swelling and erythema at the application site or at a distant site. Less common (<1%) adverse reactions included contact urticarial. There are no significant drug-drug interactions.[1,6,7,8]

Crisaborole carries a wholesale price of $580 for a 60 gram tube and is currently available on the market as of January 2017. Although it is not reserved as first line treatment, it can be an alternative therapy for patients and prescribers. Crisaborole is expensive and insurance coverage is still being negotiated; as of now, there are manufacturer coupons that allow patients to obtain their medication with no out-of-pocket expenses.[8]

Other Current Therapeutic Regimens

Current therapeutic treatments for mild to moderate eczema includes a variety of topical corticosteroids, topical calcineurin inhibitors, and device creams. Topical corticosteroids are considered the mainstay of therapy. The topical corticosteroids adverse reactions include hypothalamic-pituitary-adrenal (HPA) axis suppression (central stress response system), atrophy (muscle waste away), striae (stretch marks), and telangiectasia (spider veins). Topical calcineurin inhibitors, pimecrolimus and tacrolimus, are indicated as second-line therapy in patients who have failed other topical treatments. In 2006, a black box warning was issued in the United States for calcineurin inhibitors for increased risk of skin malignancy and lymphoma. Efficacy of the device creams, which include Atopiclair, Eletone, EpiCream, and Mimex, is modest. Despite the number of available therapies, there is need for additional therapeutic options having favorable safety profiles due to the limitations and adverse reactions with current regimens.[5]

Omalizumab and Dupilumab are two monoclonal antibodies that are availablet. Omalizumab is a monoclonal antibody that primarily blocks the function of IgE. Case reports did suggest it can be an effective treatment option for eczema. However, in a recent randomized, placebo-controlled trial, omalizumab did not demonstrate improvement of symptoms. In March 2017, FDA approved Dupixent (dupilumab), the first monoclonal antibody to be introduced to the market for eczema.[2] It is an injection that is intended to treat adults with moderate to severe eczema who are not controlled by topical therapies.[2,3] Dupilumab works by inhibiting the interleukin (IL) 4-receptor alpha. The IL 4-receptor alpha then blocks the IL-4 and IL-13 receptors, which is required to activate the Type 2 helper T-cell (Th2) immune response that causes allergic inflammation. It is administered subcutaneously weekly or bi-weekly at 300mg. In a randomized, double-blind, placebo-controlled trial, patients who received dupilumab has reported significant reduction of the inflammation within a couple of weeks.[2]

Approval of dupilumab was based on clinical trials of dupilumab monotherapy (SOLO 1 and SOLO 2) and in concomitant administration with topical corticosteroids (CHRONOS). Results from SOLO 1 (n = 671) and SOLO 2 (n = 708) trials showed 36-38% of patients who received dupilumab had scores of 0 or 1 (clear or almost clear) on the ISGA scale compared with placebo (8% to 10%) ($p < 0.001$). Additionally, improvement from baseline to week 16 of at least 75% on the Eczema Area and Severity Index was reported in significantly more patients who received each regimen of dupilumab than in patients who received placebo ($p < 0.001$). Some serious side effects that were reported were serious allergic reactions, pink eye, and inflammation of the cornea. Some common side effects were injection site reactions, cold sores, or eye and eyelid inflammation. Although dupilumab is approved for atopic dermatitis, it is also

in phase II of clinical trials for asthma. It is also being explored to treat nasal polyps and eosinophilic oesophagitis.[6]

Conclusion

In conclusion, despite the availability of standard therapies, there is a need for additional therapeutic options due to their limitations and adverse reactions. Atopic dermatitis represents a large market with a significant unmet need. The recent approvals for crisaborole and dupilumab have provided much needed treatment alternatives for patients with eczema. While dupilumab appears to be more effective, crisaborole has the advantage with respect to administration, safety, and pricing. Crisaborole is a non-steroidal topical monotherapy that does not cause skin thinning and other side effects that occur from prolonged steroid use. Therefore, it can be applied to sensitive and thin areas of the skin such as the face, eye lids, and groin. This is a great advantage and alternative for patients who are hesitant to using topical steroids due to their known side effects.[1,2,3,8]

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