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EDITORIAL

Crisaborole: Application Pain and Prevention

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Abstract: In 2016, a new drug, crisaborole, was developed and approved, for the first time in 15 years, as an effective treatment for Atopic Dermatitis (AD). Crisaborole is a topical phosphodiesterase 4 (PDE4) inhibitor, which alleviates AD symptoms, such as pruritis, inflammation, and flares. Similar to other topical treatments like corticosteroids and calcineurin inhibitors, crisaborole has been found to cause pain during application. The pain felt during a topical application can be attributed to many possible causes, such as increased sensitivity to pain-provoking and itch-provoking stimuli, prior inflammation, prior damage, and hypersensitized skin of the patient to which the topical cream is applied. Crisaborole has been reported to be effective, yet the application site pain is a major road bump in the effective treatment of some patients. Some possible ways to circumvent this pain are letting the epidermis soothe and heal before starting crisaborole, starting this treatment modality before the skin has a chance to become irritated and inflamed, and numbing the area with an ice pack prior to topical crisaborole application. Overall, crisaborole has been an effective treatment modality, but further research is necessary to allow for safe use of this life-changing AD topical medication.

Keywords: Crisaborole, Application pain, Atopic dermatitis, Pain prevention, PDE4 inhibitor, Topical treatment.

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In 2016, a new drug, crisaborole, was developed and approved, for the first time in 15 years, as an effective treatment for Atopic Dermatitis (AD) [1]. Crisaborole is a topical phosphodiesterase 4 (PDE4) inhibitor, which alleviates AD symptoms, such as pruritis, inflammation, and flares [1]. The mechanism of this drug entails a low molecular weight boron compound with optimal skin penetration and minimal interactions with a compilation of 50 receptors and ligand-gated ion channels [1 - 3]. Crisaborole competitively and reversibly inhibits the active binding site of the PDE4 enzyme [2]. This mechanism is effective because, in AD individuals, the PDE4 enzyme is overactive in inflammatory cells, causing a release of cytokines due to increased intracellular cyclic adenosine monophosphate (cAMP) degradation [4 - 10]. Molecular formulas similar to crisaborole have been used in pill forms, but this is the first scientifically supported topical treatment for inhibiting the PDE4 enzyme. A study performed by Paller *et al.* [1] found that crisaborole is an effective treatment by showing more patients achieving success on the Static Global Assessment (ISGA) scores when compared to the vehicle, as well as achieving this ISGA score earlier than the vehicle, and even having better outcomes about the clarity of the skin than the vehicle. Though statistically significant improvements have been reported with the use of this drug, it has adverse effects associated with its use, similar to its other topical therapy counterparts.

Topical corticosteroids have been the standard AD treatment. They have long term complications with prolonged use, such as skin atrophy, telangiectasias, and hypopigmentation [11]. This has pushed the pursuit for the development of other topical treatment methods without long-term consequences. Other than the commonly used topical corticosteroids, topical calcineurin inhibitors are also utilized for the treatment of AD, as well as the newly developed crisaborole. All three of these valid treatment modalities have been found to cause pain at the application site [12]. The pain felt during a topical application can be attributed to many possible causes. To begin, AD patients have been found to have an increased sensitivity to pain-provoking and itch-provoking stimuli [12]. In a study performed by Vakharia *et al.* [13], the baseline of skin pain is increased for AD patients, with 42.7% of patients experiencing skin pain in the past week [13]. This would explain the predisposition for an AD patient to experience pain upon application. However, the most simplistic attribute for causing pain is the prior inflammation, damage, and hypersensitized skin of the patient to which the topical cream is applied. This theory has been discussed even more in-depth by Draelos *et al.* [12], in which the proposed mechanisms for the AD patient's

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pain is attributed to the disruption of the epidermis through inflammation and extensive scratching, which leads to increased exposure of nerve endings [13 - 16]. Also, the nerve endings are further sensitized, increased in density, number, length, or even hypertrophied [13 - 17]. The sheer irritation of epidermal pain-transmitting nerves could be a major contributor to the sensation of pain, burning, or stinging from topical application of a medication, or more specifically, crisaborole. This idea of the irritated epidermis contributing to application site pain was further supported by the two studies performed by Paller *et al* [1]. and Lin *et al.* [18]. Paller *et al.* [1] found a 4.4% rate of application site pain with the mean age of this study being 12.2 years including the crisaborole and vehicle-treated. The young age of the subset of patients allowed for less years of scratching, damage, and constant inflammation to the skin that was receiving the topical crisaborole. Young age may be a protective factor for not experiencing application pain. In the study performed by Lin *et al.* [18], the rate of pain at the application site was 31.7%, with an average age of the patients being 35.9 years. This drastic increase in application site pain in Lin *et al.* [18] study compared to Paller *et al.* [1] study may be attributed to many different beliefs, but a prominent theory is the years of damage to the patient's skin being radically higher in the study by Lin *et al.* [18]. The older patient sample in the study by Lin *et al.* [18] may have allowed for a longer period of exposure of the free nerve endings, as well as increased time to develop sensitization to different external stimuli to cause pain.

Crisaborole has been reported to be effective, yet the application site pain is a major road bump in the effective treatment of some patients. The extent of this issue has been found to be of greatest concern particularly on the first day of treatment. In the study by Paller at al [1], 76.7% of the patients who experienced application pain felt it on the first day, with 77.6% of those patients having a resolution within 1 day of pain onset. A possible way to overcome this barrier could be prophylactic treatment before initial topical application. This is especially helpful for patients who have severe skin irritation, have had previous adverse reactions to topical ointments, or excessively fear pain. One such prophylactic approach may involve allowing the epidermis to soothe and heal before starting crisaborole. This could entail frequent emollient and moisturizer application, and refraining from scratching or other inflaming activities. A way to allow for this healing process to take place could be the application of anti-pruritic topical ointments such as Pramoxine, which provide relief through acting on the unmyelinated nerve endings in the dermis [17]. This would prevent epidermis irritation, stratum corneum alteration, the release of cytokines, and soothe the sensitized nerve endings [17]. A second prophylactic option may involve starting this treatment modality before the skin has a chance to become irritated and inflamed. In the study by Paller *et al.* [1], the average age of the participant was 12.2 years, and showed a much lower rate of pain at the application site than other studies, such as Lin *et al.*'s [18] report, with an older age group of an average age of 35.9 years. This lower rate of pain may be attributed to less damage to the epidermis, healthier skin, and fewer years of irritation in a younger patient subset. If this treatment modality was begun at a young age and continued, it may have the same beneficial results without the application pain adverse effect. The last possible prophylactic treatment idea to prevent application pain may include numbing the area before application. Since the pain, stinging, and burning seems to be localized to the first day, the numbness would only need to be induced for a short time period. Though localized lidocaine injections are possible, a more realistic option could be icing the area to numb it. This would allow the patient to control the area of application, as well as control their sensitivity to the topical crisaborole. This prophylactic method could also be able to be performed at home with twice daily application. Overall, crisaborole has been an effective treatment modality, but further research is necessary to allow for safe use of this life-changing AD topical medication.

LIST OF ABBREVIATIONS

AD	=	Atopic Dermatitis
PDE4	=	Phosphodiesterase 4
cAMP	=	Cyclic Adenosine Monophosphate
ISGA	=	Static Global Assessment

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