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Clinical Evidence Supporting the Use of Crisaborole in Vitiligo

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Abstract:

Crisaborole is a topical non-steroidal phosphodiesterase-4 (PDE4) inhibitor that has gained increasing attention in dermatology due to its anti-inflammatory and immunomodulatory properties. It was first approved for the treatment of mild to moderate atopic dermatitis, where it reduces inflammatory cytokine production through elevation of intracellular cyclic adenosine monophosphate (cAMP). Beyond its approved indication, emerging evidence suggests potential therapeutic roles for crisaborole in several dermatologic conditions, including psoriasis, seborrheic dermatitis, contact dermatitis, and vitiligo. Recent studies have highlighted its favorable safety profile, minimal systemic absorption, and suitability for long-term topical use, particularly in sensitive skin areas. Additionally, inhibition of PDE4 may modulate inflammatory pathways and promote melanocyte survival and melanogenesis, providing a theoretical basis for its use in vitiligo management. This mini-review summarizes the pharmacology, mechanism of action, clinical applications, and emerging evidence regarding the role of crisaborole in dermatologic diseases, with particular emphasis on its potential role in vitiligo.

Keywords: Crisaborole; Phosphodiesterase-4 inhibitor; Atopic dermatitis; Vitiligo; PDE4; Dermatology; Topical anti-inflammatory therapy.

Introduction:

Crisaborole is a non-steroidal, small molecule, boron-based compound that selectively inhibits Phosphodiesterase-4 (PDE4), particularly the PDE4B and PDE4D isoforms, prevalent in inflammatory skin diseases Phosphodiesterase-4 inhibitor (PDE4I) was initially approved by the U.S. Food and Drug Administration (FDA) for the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients in December 2016 for patients 2 years and older. Its use was then expanded in March 2020 following clinical trials, which demonstrated its safety and efficacy in infants as young as 3 months **(1).**

Pharmacokinetics of Crisaborole:

In a study conducted by **Zane et al., (2)** on 34 pediatric patients (2 to 17 years) with mild to moderate atopic dermatitis, Crisaborole 2% ointment was applied at approximately 3 mg/cm² twice daily for eight days. The time to reach maximum plasma concentration (Tmax) remained consistent, over the 8-day period, at approximately 3 hours, with a range of 3 to 24 hours. Steady-state systemic concentrations were achieved by day 8 of treatment.

Crisaborole exhibits a high degree of plasma protein binding, with approximately 97% bound to human plasma proteins. It undergoes extensive metabolism to two major inactive metabolites. The primary metabolite, 5-(4-cyanophenoxy)-2-hydroxyl benzyl alcohol, is formed via hydrolysis and is further oxidized to 5-(4-cyanophenoxy)-2-hydroxyl benzoic acid**.** The elimination of the drug occurs primarily through the renal route **(3).**

Dosage and administration of Crisaborole:

Crisaborole is formulated as a 2% ointment for topical use, typically applied in a thin layer twice daily to affected areas. No dose adjustments are recommended for patients with hepatic or renal impairment. There is limited safety data for use in pregnancy, lactation, or geriatric populations **(3).**

An ex-vivo study by **Draelos et., al (4)** examining co-application with emollients showed that Crisaborole penetrated the skin most effectively when applied at least 15 minutes before the emollient, highlighting the importance of proper application sequence to maximize efficacy and minimize local adverse effects such as stinging or burning sensations**.**

Safety and Tolerability

Crisaborole is generally well-tolerated, with mild and transient side effects such as erythema, itching, or burning at the application site. These side effects are common with topical therapies and are often manageable. Unlike systemic PDE4 inhibitors, Crisaborole does not cause significant gastrointestinal side effects due to its limited systemic absorption **(5).**

Uses of Crisaborole in dermatology

Atopic dermatitis (FDA approved indication):

Crisaborole functions as a small-molecule inhibitor of phosphodiesterase 4 (PDE4), an intracellular enzyme that promotes the release of cytokines such as IL-4, IL-5, IL-13, and IFN-γ which contributes to immune dysregulation and skin barrier dysfunction in patients with atopic dermatitis. By inhibiting PDE4, crisaborole prevents the breakdown of cAMP. Elevated levels of cAMP lead to a reduction in the production of these pro-inflammatory cytokines, resulting in decreased inflammation and itching, providing relief to patients suffering from atopic dermatitis **(6)**.

Crisaborole is effective for mild to moderate atopic dermatitis (AD) in patients aged 3 months and older. Studies demonstrated significant reductions in AD severity, with improvements in erythema, exudation, and lichenification. A phase IV study in infants (3–24 months) showed that 16.1% of the subjects reported adverse events, primarily mild application site reactions. Long-term studies (up to 52 weeks) indicate greater flare-free days with Crisaborole compared to vehicle, with minimal discontinuations due to adverse effects **(7)**

Off label therapeutic potentials: table (1)

Condition	Study type	Key Findings	Reference
Psoriasis	Case Reports	Successful treatment of refractory palmoplantar psoriasis in a 50 year old woman	**(8)**
	Case Reports	Successful treatment of a case with refractory facial, groin and inflammatory psoriasis with notable improvement after just 12 days of treatment.	**(9)**
	Randomized controlled trial (RCT),	66% target lesion severity scale (TLSS) improvement in intertriginous/facial/anogenital psoriasis (RCT, n=21).	**(10)**
Seborrheic Dermatitis (SD)	Case Report	Marked improvement in the erythema/scaling in a 50 year old woman with chronic bilateral nasolabial fold SD in comparison to moisturizer CeraVe.	**(11)**

	Prospective open-label clinical trial	83.3% achieved clear/almost clear status in mild to moderate facial SD (n=30, 4 weeks).	**(12)**
Inflammatory Linear Verrucous Epidermal Nevus (ILVEN)	Case Reports	Successful reduction in pruritus, erythema, and lesion flattening in pediatric patients (aged 5, 9), after other treatments failed.	**(13)**
Vulvar Leukoplakia	Randomized controlled trial (RCT)	92% response rate in vulvar lichen simplex chronicus/ sclerosus vs. 52% with vitamin E (n=100, 2 weeks). Mild local pain and ulceration in 2/50 cases appling Crisaborole ointment.	**(14)**
Morphea	Pilot Study	Reduced dermal fibrosis in 5/7 patients, clinical improvement in 6/7 after 12 weeks. It can be used in steroid-refractory cases.	**(15)**
Chronic Hand Eczema	Retrospective Review	72.2% symptom improvement in 251 patients.	**(16)**
Stasis Dermatitis	Randomized controlled trial	Significant reduction in total sign score (TSS) vs. vehicle (n=65, 6 weeks).	**(17)**
Alopecia Areata	Theoretical (No Case Reports)	Suggested for limited patches due to elevated PDE-4 in scalp lesions. No clinical data	**(18)**
Allergic contact dermatitis	Case Report	Marked improvement in facial allergic contact dermatitis in 68-year-old woman with history of rosacea within 2 weeks after corticosteroid failure, without aggravation of her rosacea.	**(19)**
Irritant Contact Dermatitis	Case Report	Resolution in 29-year-old nurse with hand dermatitis within 8 weeks. Well-tolerated.	**(19)**
Knuckle Pads	Case Report	Asymptomatic plaques resolved in 45-year-old man within 2 weeks. Novel treatment option.	**(20)**
Necrobiotic Xanthogranuloma (NXG)	Case Report	Complete response in a patient with NXG and multiple myeloma.	**(21-24)**

Crisaborole in vitiligo:

Clinical evidence supporting the use of Crisaborole in Vitiligo:

The first published evidence linking PDE4 inhibitors to the treatment of vitiligo was a 2017 case report by **Huff and Gottwald (25)** that described significant repigmentation in a case of chronic, recalcitrant vitiligo treated with apremilast, an oral PDE4 inhibitor.

The clinical evidence for Crisaborole in vitiligo is primarily derived from case reports, which indicate its potential to induce repigmentation in treatment-resistant cases. The first documented use of Crisaborole in vitiligo dates back to 2019, with a published case report by **Tausends et al. (22)** which described partial perifollicular pigmentation observed in a Hispanic male in his 40s with persistent vitiligo for more than 20 years, after one months of twice daily application of 2% crisaborole to the ears, with no side effects noted during the treatment course. The patient had previously been treated with topical steroids and calcineurin inhibitors without satisfactory improvement. Since then Since then, a few additional case reports and small series have noted its off-label usage in vitiligo, but the number of published studies remains very limited

Tam et al. (23) described a 71-year-old man with generalized vitiligo and a history of atopic dermatitis. His prior therapies included clobetasol 0.05% ointment and tacrolimus 0.1% ointment. Treatment with 2% crisaborole ointment, applied twice daily to the hands, led to significant repigmentation and halted disease progression. The patient continued the regimen for 22 months without experiencing any adverse effects.

Sun et al. (24) presented the case of a 47-year-old woman with an 18-year history of generalized vitiligo. She had undergone multiple treatments including halometasone 0.05% cream, tacrolimus 0.1% ointment, narrowband UVB phototherapy, and oral Chinese medicines. After initiating 2% crisaborole ointment applied twice daily to the face, she achieved near-total clearance of facial lesions, with her F-VASI score improving from 3.49 to 0.34 over a 4-month period. No side effects were reported.

In the same study, **Sun et al. (24)** also reported an 18-year-old woman with segmental vitiligo affecting the eyebrow for eight months. She had previously been treated with 308-nm excimer laser and tacrolimus 0.1% ointment. The introduction of 2% crisaborole ointment applied twice daily to the eyebrow resulted in 70% repigmentation after four months, although there was no improvement in leucotrichia. No side effects occurred during therapy.

A case-control study by **Nagui et al. (26)** demonstrated significantly higher PDE4 levels in the lesional skin and serum of vitiligo patients compared to controls. This suggests that PDE4 overexpression may exacerbate inflammatory pathways in vitiligo, making PDE4 inhibition a rational therapeutic strategy.

Mechanism of action of Crisaborole in vitiligo

Crisaborole's mechanism of action in vitiligo centers on its anti-inflammatory, immunomodulatory and melanogenesis promoting effects through its ability to inhibit PDE4, leading to an increase in the cAMP signaling pathways **(27).** Its low molecular weight (251 Da) and lipophilicity enable penetration through the stratum corneum, ensuring localized delivery with minimal systemic absorption **(28).**

Anti-inflammatory and immunomodulatory effect

Crisaborole works by inhibiting the enzyme phosphodiesterase-4 (PDE4), which is responsible for breaking down cyclic adenosine monophosphate (cAMP) into adenosine monophosphate (AMP). The inhibition of PDE4 results in elevated intracellular cAMP levels in immune cells and skin cells. Increased cAMP activates protein kinase A (PKA), which phosphorylates downstream targets, including the transcription factor cAMP response element-binding protein (CREB). This activation modulates gene expression, promoting anti-inflammatory pathways and inhibiting pro-inflammatory transcription factors such as nuclear factor-kappa B (NF-κB), reducing the transcription of pro-inflammatory cytokines **(29).**

Crisaborole suppresses the production of TNF-α, IL-12, IL-17, IL-23, and IFN-γ, which are critical drivers of Th1 and Th17 activity in vitiligo**.** This reduction in pro-inflammatory cytokines decreases the recruitment and activation of cytotoxic T cells and NK cells, reducing melanocyte destruction **(30).** Concurrently, Crisaborole enhances the expression of anti-inflammatory cytokines, including interleukin-2 (IL-2) and interleukin-10 (IL-10), which counteract the autoimmune attack on melanocytes **(23).**

Pro-melanogenic effect

The cAMP signaling promotes melanocyte differentiation and proliferation, which are essential for repigmentation, through the activation of PKA and CREB, which in turn promote the transcription of

microphthalmia-associated transcription factor (MITF) a critical regulator of melanogenesis and cellular defense against oxidative stress. This signaling cascade works through the melanocortin-1 receptor (MC1R), which is turned on by α-melanocyte-stimulating hormone (α-MSH). **(31) (Figure 1).**

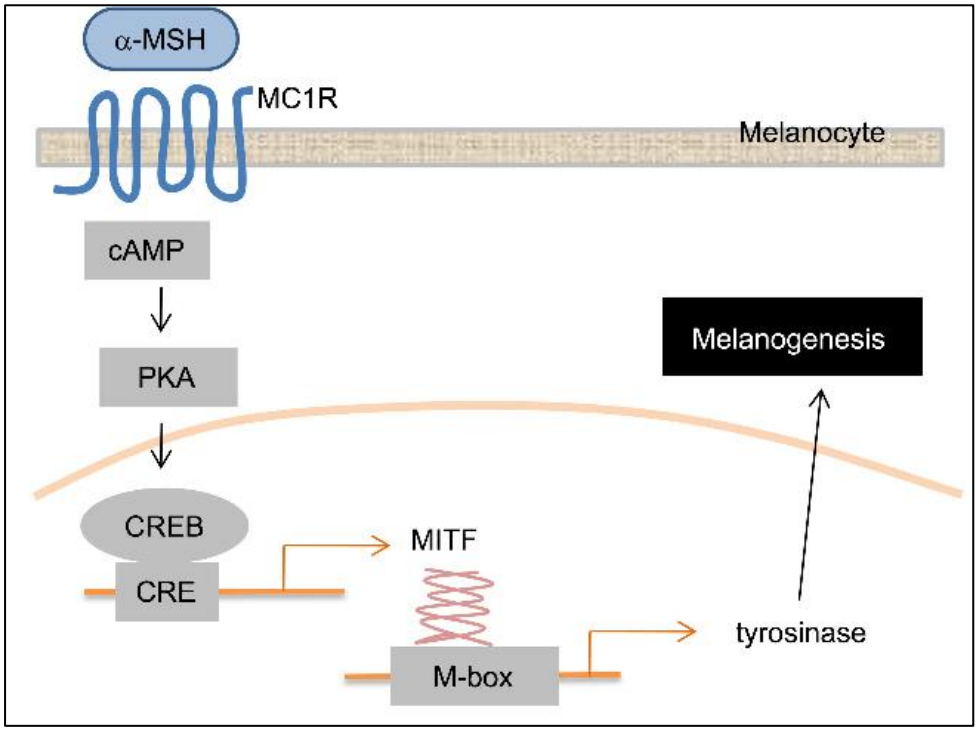

Figure (1): Melanogenesis signaling cascade **(32)**

Comparison with systemic PDE4 Inhibitors

Crisaborole's topical application offers advantages over systemic PDE4 inhibitors like Apremilast, which has been studied for vitiligo but is associated with systemic side effects. **Majid et al., (33)** studied 30 adults with rapidly progressive non-segmental vitiligo (NSV) involving 4–30% body surface area, all of whom were unresponsive or intolerant to conventional systemic therapies. After three months of oral apremilast at a dose of 30 mg twice daily, 96.3% of patients achieved stabilization of disease activity, while 70.3% demonstrated partial repigmentation across multiple body sites, including acral lesions in 37% of cases. Gastrointestinal side effects such as headache, nausea, and abdominal pain were reported in a few patients, leading to treatment discontinuation in some instances.

Khemis et al., (34) conducted a randomized trial involving 77 patients who received apremilast with narrowband ultraviolet B (NB-UVB) compared to NB-UVB with placebo. Over two 24-week treatment periods, apremilast failed to show additional benefit beyond phototherapy alone. Reported side effects in this study included diarrhea, abdominal discomfort, and headache.

Apremilast demonstrated partial repigmentation in case series (e.g., 8 of 13 patients showed repigmentation after 3 months), but a randomized controlled trial found no added benefit when combined with NB-UVB **(34).** In contrast, localized application of Crisaborole minimized systemic side effects, making it suitable for long-term use and for sensitive areas. However, its efficacy in larger, controlled studies remains to be established **(24).**

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