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REVIEW ARTICLE

Crisaborole: a dermatologic perspective

Crisaborole: uma perspectiva dermatológica

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Abstract

Crisaborole is a non-steroidal boron-containing topical phosphodiesterase-4 inhibitor that has been approved by the US-FDA for the treatment of atopic dermatitis in children (> 3 months of age) and adults. More recently, its efficacy has been outlined in the treatment of many other dermatoses, including vitiligo, psoriasis, morphea, seborrheic dermatitis, stasis dermatitis, and vulvar leukoplakia, to name a few. While crisaborole represents a valuable non-steroidal alternative in dermatological therapy, the primary limitation is its high cost compared to other topical agents. Nevertheless, despite this limitation, its use in recalcitrant cases can be worth considering.

Keywords: Crisaborole. Atopic dermatitis. Psoriasis. Vitiligo. Morphea.

Resumo

O crisaborole, é um inibidor tópico não esteroide da fosfodiesterase-4 contendo boro, aprovado pelo US-FDA para o tratamento de dermatite atópica em crianças depois dos 3 meses de idade e adultos. Ultimamente, a sua eficácia foi reportada no tratamento de muitas outras dermatoses, incluindo vitiligo, psoríase, morfeia, dermatite seborreica, dermatite de estase e leucoplasia vulvar, para citar algumas. Embora o crisaborole represente uma alternativa não esteroidal valiosa na terapia dermatológica, a principal limitação é seu alto custo em comparação a outros agentes tópicos. No entanto, apesar dessa limitação, seu uso em casos recalcitrantes pode valer a pena ser considerado.

Palavras-chave: Crisaborole. Dermatite atópica. Psoríase. Vitiligo. Morfeia.

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Introduction

Crisaborole is a boron containing topical phosphodiesterase-4(PDE4) inhibitor approved by the FDA for topical treatment of mild to moderate atopic dermatitis (AD) in patients aged 3 months or older[1,2]. The presence of the boron atom in crisaborole facilitates drug penetration through human skin, thus enhancing its dermal concentrations[1]. Although, initially used as a non-steroidal topical drug for AD, crisaborole has demonstrated benefit in the management of various other dermatological disorders. This review will comprehensively elucidate the utility of crisaborole in AD, as well as other dermatoses.

Pharmacokinetics

Following twice daily crisaborole application, maximum plasma concentrations are achieved within 3-24 h, with steady state systemic concentrations available by 8 days, along with a mean accumulation factor of 1.9[3]. The drug is 97% bound to plasma proteins, and metabolized into two inactive metabolites. The major metabolite is 5-(4-cyanophenoxy)-2-hydroxyl benzyl alcohol, which is further oxidized to produce the other metabolite, 5-(4-cyanophexy)-2-hydroxylbenzoic acid. Both metabolites attain steady-state systemic concentrations by day 8 of crisaborole initiation. Major route of drug elimination is through the kidneys[3].

Mechanism of action

Crisaborole inhibits the enzyme PDE4 in a competitive and reversible way; a schematic representation of which is outlined in figure 1[4]. Crisaborole inhibits PDE4, an enzyme that breaks down cyclic adenosine monophosphate (cAMP). By inhibiting PDE4, crisaborole increases intracellular cAMP levels, which subsequently activates protein kinase A (PKA). This activation leads to phosphorylation of the transcription factor CREB (cAMP response element-binding protein) and inhibition of nuclear factor-κB. These molecular changes ultimately result in decreased production of pro-inflammatory cytokines (including tumor necrosis factor [TNF]-α, Interleukin [IL]-2, IL-4, IL-5, IL-23, and Interferon-gamma [IFN-γ]) and increased production of anti-inflammatory cytokines (such as IL-10). The presence of boron in crisaborole's structure enhances skin penetration by forming a reversible bond with the hydroxyl groups in the stratum corneum, allowing more efficient dermal delivery of the active compound.

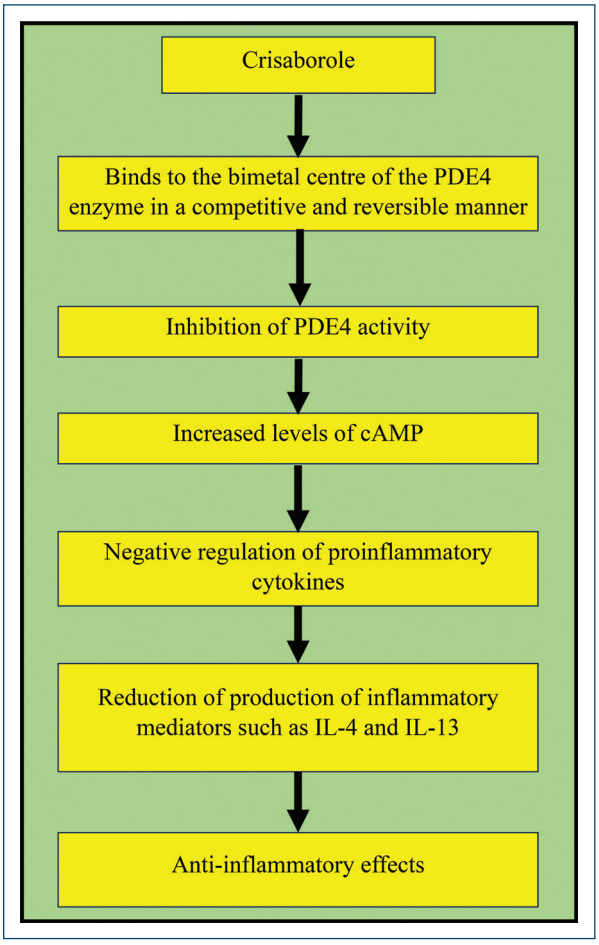

Figure 1. Mechanism of action of crisaborole.

Clinical uses

Atopic dermatitis

AD is a chronic endogenous eczema, typically known for its relapsing and remitting course. Although topical corticosteroids (TCSs) are still considered the mainstay of AD treatment, their long-term usage is not recommended due to adverse effects, namely, skin atrophy, telangiectasia, striae, as well as suppression of the hypothalamo-pituitary adrenal axis, which is often a concern in pediatric patients[2]. To counter these adversities, it becomes essential to use an alternative drug that is effective, as well as safe for long-term treatment. Although, topical calcineurin inhibitors (TCIs) such as tacrolimus and pimecrolimus hold value in the treatment of AD, newer agents in the therapeutic arsenal of AD are always welcome. Crisaborole offers yet another option in this category, with a different mechanism of action, demonstrating efficacy, without the side effects of TCS.

Table 1. Studies outlining the benefits of crisaborole in atopic dermatitis

No.	Authors	Study type	Details	Remarks
1	Paller et al.[1]	Two double-blind, vehicle-controlled phase 3 trials (AD-301; AD-302) in 1527 patients aged 2-79 years.	Randomization to crisaborole (n = 763) or vehicle (n = 764) twice daily for 28 days.	Better treatment response for crisaborole (Trial 1: 32.8% vs. 25.4%; p = 0.038, Trial 2: 31.4% vs. 18%; p < 0.001). IGA Score 0/1 more frequent with crisaborole (Trial 1: 51.7% vs. 40.6%; p = 0.005; Trial 2: 48.5% vs. 29.7%; p < 0.001). Statistically significant improvement in pruritus, and AD lesions.
2	Zane et al.[7]	Phase Ia open-label to assess efficacy of 2% crisaborole ointment in 34 AD patients aged 2-17 years.	Crisaborole ointment twice daily for 28 days.	IGA score of 0 (clear) or 1 (almost clear) in 64.7%. Improvements in erythema (–64.9%), excoriation (–58.2%), exudation (–64.3%), pruritus (–63.3%) lichenification (–61.3%).
3	Murrell et al.[8]	Double-blind phase II trial in 25 adults aged 18-75 years with mild to moderate AD.	All patients treated with crisaborole Q12H or vehicle for 28 days, each to one of the two target lesions. All patients had two target lesions, with one treated with crisaborole ointment twice daily and the other with vehicle for 28 days in a split-body design.	68% of patients with greater reduction in AD severity index scores for the lesion treated with crisaborole versus vehicle.
4	Eichenfield et al.[9]	Randomized, double-blind, vehicle controlled, phase III study 270 patients aged 3 months-18 year.	Group 1 (n = 135) - crisaborole Q12H for 52 weeks Group 2 (n = 135) vehicle Q12H for 52 weeks.	At 52 weeks the mean number of flares and mean number of flare free days significantly lower in Group 1 (34.6 days difference).
5	De et al.[10]	4-week open label study on 19 mild-to-moderate AD (aged 2-16 years).	2% crisaborole ointment Q12H for 30 days.	IGA reduction from 2.58 ± 0.61 to 0.095 ± 0.78 (p < 0.001). Pruritus score reduced from 2.32 ± 0.478 to 0.84 ± 0.60 (p < 0.001). Statistically significant improvement in AD lesions.
6	Schlessinger et al.[11]	Phase IV open label study (CrisADe CARE 1).	137 infants with mild-to-moderate AD 3-24 months' old Crisaborole Q12H for 28 days.	Adverse events in 22 patients (16.1%): site discomfort (2.9%), erythema (2.9%); and site pain (3.6%).

Although, the exact mechanism of crisaborole in AD is incompletely understood, following topical treatment, studies have shown decreasing levels of AD biomarkers on lesional biopsy specimens from day 0 to 8 and 15 and significant downregulation of genes involved in Th2, Th17 and Th22 pathways, with consequent reduction in the production of inflammatory mediators[5]. Moreover, higher levels of PDE4 have been identified in AD patients, and inhibition of PDE4 by crisaborole in monocytes reduces pro-inflammatory cytokines[6]. This manifests clinically as a rapid and persistent improvement in pruritus and a reduction of AD associated signs and symptoms, as early as the 1st week of treatment. Besides, as pruritus is reduced, the itch-scratch cycle is broken, which is associated with improvement in the quality of life (QoL) in these patients.

However, despite treatment success in approximately 31-47% of AD patients with ~49-65% investigator static global assessment scores of clear or almost clear in clinical trials, crisaborole still remains a second-line topical agent for AD behind TCS and needs to be reserved for patients unresponsive or unable to use TCS. Various studies on the utility of crisaborole in AD are outlined in table 1[1-7,11].

Vitiligo

Nagui et al.[12], in their study, outlined significantly higher levels of PDE4 in the skin and serum of vitiligo patients compared to controls ($p < 0.001$), suggesting PDE4 to play a role in disease pathogenesis. Inhibition of PDE4 is associated with elevated levels of cAMP that suppresses expression of TNFα, IL-23, and IFNγ, along with an increase in IL-10 and IL-12 (anti-inflammatory mediators), and in this way halts perpetuation of the inflammatory process in vitiligo[13]. Furthermore, the cAMP pathway has shown to promote melanogenesis by inducing melanocyte differentiation and proliferation[14]. Based on these findings, crisaborole (2%) ointment has been used for vitiligo.

Tam et al. outlined the beneficial role of crisaborole in a 71-year-old man with vitiligo involving his forearm and dorsal aspect of hands unresponsive to clobetasol propionate (0.05%) and tacrolimus (0.1%). Notable re-pigmentation of the vitiliginous patches was evident within 10 months of crisaborole use, and by 22 months, repigmentation further increased, along with control of disease progression[15].

In another report, crisaborole was beneficial in promoting repigmentation of persistent vitiligo over the ears in a Hispanic male in his 40's, who had failed to respond to TCS and TCIs. Within 1-month of treatment, scattered areas of perifollicular pigmentation was witnessed over both ears[16]. Both patients tolerated treatment well, with no adverse effects.

Based on these reports, crisaborole may serve as a potential option in vitiligo with minimal body surface area involvement. Further, combination of crisaborole with phototherapy and microneedling are other avenues for future research[15,16].

Psoriasis

The role of PDE4 in the pathogenesis of psoriasis is clearly demonstrated and, apremilast, an oral PDE4 antagonist has been well established in psoriasis therapeutics, with its approval in moderate-to-severe plaque psoriasis and psoriatic arthropathy. Once PDE4 is blocked, release of multiple inflammatory mediators including TNFα, IFNγ, IL-1β, IL-2, IL-5, and IL-6 and various chemokines are decreased, thus contributing to disease regression[17].

Topical therapy in psoriasis demonstrates greater clinical efficacy in anatomical sites with thin non-scaly plaques, given the thickness of stratum corneum being inversely proportional to drug absorption[18]. Thus facial, anogenital and intertriginous sites serve as favorable targets for the trial of newer agents.

Hashim and col. in a double-blind, randomized, and vehicle-controlled study evaluated the utility of crisaborole (2% ointment applied twice daily [Q12H]) as monotherapy for intertriginous, facial and anogenital psoriasis. Following 8 weeks of treatment, there was an 81% change of the target lesion severity scale in patients receiving crisaborole; with 71% of participants achieving lesional clearance. In addition, there were no reports of adverse skin reactions at the application sites[18].

Despite the favorable profile of crisaborole in psoriasis in this report, more studies are ongoing to confirm the benefit of crisaborole. Further, its use in combination with TCS both as continuous and pulse therapy needs evaluation.

Morphea

Morphea, also referred to as localized scleroderma, is a clinical condition characterized by skin and soft-tissue inflammation and sclerosis.

In a single-arm, open-label, pilot study of seven adult patients with active morphea involving < 20% total body surface area, unresponsive to TCS, crisaborole 2% ointment applied twice daily for 12 weeks induced histologic reduction of dermal fibrosis in five of seven patients, and clinical reduction in size of treated plaques among six of seven patients, at the end of treatment[19].

Reduction of dermal fibrosis by crisaborole in morphea may be linked to its ability in interfere with the release of IL-6 from M2 macrophages[20]. Though promising, more studies are required to assess the utility of crisaborole in morphea.

Seborrheic dermatitis

In seborrheic dermatitis (SD) PDE4 inhibitors have been studied as a potential new approach. These drugs outline their effects in SD by increasing levels of cAMP and suppressing pro-inflammatory molecules[21]. The utility of crisaborole 2% ointment, following twice weekly applications for 4 weeks in treating chronic SD of the nasolabial folds, was first emphasized by Lui et al. in an individual case report. Following completion of treatment, notable reduction in scaling and erythema was witnessed[22].

This was followed by the communication of Peña et al.[23], who highlighted the efficacy of crisaborole (2% ointment Q12H application) in treating mild/moderate

facial SD in 30 patients aged 18–80 years. Following 1 month of treatment, in 83.3% patients, significant reduction of the Investigator Global Assessment Scale to clear or almost clear was reported, along with improvement in erythema, scaling, dryness, and pruritus. All patients tolerated the treatment well, except for one, who discontinued therapy due to headache and facial pain at week 2 of treatment. Randomized controlled trails are therefore warranted to confirm the use of crisaborole in SD, and whether its combination with other topical/systemic drugs would be more beneficial.

Stasis dermatitis

Stasis dermatitis (SDe) is a chronic inflammatory dermatosis associated with venous insufficiency. Since inflammation plays a central role in the pathogenesis of SDe, targeting inflammation represents a logical therapeutic strategy[24]. By blocking PDE4, crisaborole helps reducing production of inflammatory cytokines which may prove beneficial in treating SDe[25].

In a randomized, proof-of-concept phase 2a study, crisaborole 2% ointment applied Q12H (n = 33) versus vehicle (n = 32) was assessed in patients with SDe unresponsive to TCS, TCIs or compression garment. Following 6-weeks of treatment, the total sign score had significantly reduced from baseline in subjects treated with crisaborole versus vehicle (–52.5% vs. –10.3%; p = 0.0004). Treatment was tolerated well in most patients, with none of them discontinuing treatment due to adverse effects secondary to crisaborole. Treatment-emergent adverse events (TEAEs) were observed in 43.8% of participants receiving vehicle treatment and 39.4% of those receiving crisaborole. Most common TEAEs with crisaborole were dermatologic that included pruritus (n = 3; 9.1%), erythema (n = 2; 6.1%), and contact dermatitis (n = 2; 6.1%). Other notable TEAEs experienced with crisaborole were urinary tract infection (n = 2; 6.1%) and headache (n = 2; 6.1%). Serious/severe adverse events occurred in 3% (n = 1) of crisaborole-treated participants, compared to 12.5% (n = 4) of vehicle-treated subjects[25]. Although promising, more research is warranted with crisaborole for SDe.

Vulvar leukoplakia

Vulvar leukoplakia (VL) is a vulvar skin disease characterized with pruritus, vulvar skin hypopigmentation, and epidermal hyperkeratosis; and dermal inflammatory infiltrates characterizing the hallmark histological profile[26].

In a prospective, randomized controlled clinical trial with 2 groups of VL patients (50 each) receiving either crisaborole 2% ointment Q12H or topical vitamin E Q12H, an effective response rate of 92% for crisaborole versus 52% for vitamin E was observed at 2 weeks of treatment. Two patients receiving crisaborole complained of local pain and ulceration that subsided after crisaborole withdrawal. No such adverse effects were reported with vitamin E[26].

Suggested mechanism of crisaborole in VL is associated with its anti-inflammatory effects following PDE4 blockade with resultant cAMP elevation, and subsequent blockade of TNFα, IFNγ, and IL-2[26].

Inflammatory linear verrucous epidermal nevus (ILVEN)

Crisaborole may be of value in the treatment of ILVEN due to the possible involvement of cellular immunologic processes in its pathogenesis.

Barney et al.[27], successfully treated a 5-year-old boy with crisaborole (2% ointment Q12H application), with no side effects.

In another report, a 9-year-old girl who had failed prior treatment with TCS, pimecrolimus and calcipotriene, responded favorably with crisaborole 2% ointment[28].

Besides, as crisaborole exhibits good safety, it can be used for a longer duration, which can be a promising new therapeutic option in ILVEN.

Knuckle pads

Knuckle pads (KPs) represent zones of fibrotic skin thickening over the knuckles and are mainly a clinical diagnosis. Crisaborole (2% ointment Q12H application) demonstrated efficacy in a 45-year-old man with a 6-year history of KPs involving the knuckles and ankles, unresponsive to intralesional triamcinolone and topical clobetasol. Within 2 weeks of crisaborole use, combined with triamcinolone acetonide and neomycin plaster, remarkable improvement was witnessed[29]. This was attributed to the ability of crisaborole to inhibit hyperkeratosis and fibroblast chemotaxis as a result of its PDE4 antagonizing property, with its boron containing structure, enhancing penetrability[29]. Nonetheless, the contributory anti-inflammatory role of triamcinolone acetonide and the occlusive environment provided by

the patch in promoting skin softening by improving medication permeability cannot be undermined.

Chronic hand dermatitis

In a retrospective review involving 251 patients with chronic hand dermatitis (CHD), crisaborole induced improvement of symptoms in 72.2% of patients after 4 weeks of treatment, with an average reduction of 43% in symptom severity as measured by the hand eczema severity index. As TNFα and IFNγ are involved in the pathophysiology of CHD, by blocking PDE4, crisaborole subsequently inhibits these proinflammatory mediators, and elevates IL-10 (an anti-inflammatory cytokine), contributing to improvement in CHD[30].

Further in a patient with hand dermatitis following frequent use of a hand sanitizer, 2% crisaborole ointment helped lesion resolution within 8 weeks of treatment, with no adverse effect[31].

Necrobiotic xanthogranuloma

In an anecdotal report, crisaborole 2% ointment was reported to bring about complete resolution of necrobiotic xanthogranuloma in a patient with associated multiple myeloma. The exact mechanism though remains elusive[32].

Lichen simplex chronicus

The beneficial role of crisaborole was shown in a 15-year-old girl with *lichen simplex chronicus* of the right posterolateral ankle refractory to topical steroids. Significant resolution was observed at 2-week, 2-month, and 5-month of follow up and was considered to be due to anti-inflammatory properties of crisaborole[33].

The level of evidence for the use of crisaborole for various dermatologic indications is represented in table 2.

Table 2. Level for evidence for the use of crisaborole in various dermatoses

Serial no.	Indications in dermatology	Level of evidence for crisaborole use
1	Atopic dermatitis	A
2	Vitiligo	E
3	Psoriasis	C
4	Morphea	D
5	Seborrheic dermatitis	B
6	Stasis dermatitis	B
7	Vulvar leukoplakia	B
8	Inflammatory linear verrucous epidermal nevus	E
9	Knuckle pads	E
10	Chronic hand dermatitis	B
11	Necrobiotic xanthogranuloma	E
12	Lichen simplex chronicus	E

A: double blind study: at least one prospective randomized double blind controlled trial without major design flaws; **B:** clinical trial with 20 or more subjects: prospective clinical trials with 20 or more subjects, trials lacking adequate controls or another key facet design, which would normally be considered desirable; **C:** clinical trial with < 20 subjects: small trials with < 20 subjects with significant design limitations, very large number of case reports (at least 20 such in literature); **D:** series of 5 or less subjects: series of patients reported to respond with at least five reports of the same in literature; **E:** anecdotal case reports.

Adverse effects

The most common adverse effects seen with crisaborole are mild-to-moderate stinging and burning that generally resolve within 24 h in most patients[2].

Dosage and administration

Crisaborole 2% ointment is given as a Q12H application schedule, with no dose adjustment in patients with hepatic/renal impairment[3]. If concomitant use of an emollient is needed, the patient should apply crisaborole at least 15 min before emollient use, to obtain maximal efficacy[34]. Emollients also help reducing stinging and burning following crisaborole use[34].

Use in special populations

Regarding the use of crisaborole in pregnancy and lactation, data are scant. However, animal studies have not indicated a cause for concern. Similarly, for patients aged ≥ 65 years, there are insufficient data determining whether geriatric patients respond differently from younger patients[3].

Drug interactions

Riociguat, a soluble guanylate cyclase stimulator is contraindicated with both non-selective PDE4 and PDE5 inhibitors due to the potential of these

medications to enhance the hypotensive effect of riociguat[35]. While this interaction is documented for systemic PDE inhibitors, the risk with topical crisaborole is minimal due to limited systemic absorption. Nevertheless, caution is advised in patients receiving riociguat.

Cost-effectiveness

The cost-effectiveness of crisaborole is a major consideration in clinical practice. With an average wholesale price of approximately $580-650 (for a 60g tube), crisaborole is considerably more expensive than generic topical corticosteroids (ranging from $10 to 50/tube) and slightly more expensive than TCIs ($200-300/tube). Due to the higher cost of crisaborole, it's use as an alternative steroid sparing drug may be a limiting factor in developing countries[36].

Future direction

The role of crisaborole in mono- or combination therapy, as well as pulse therapy with TCS (using crisaborole on weekdays, and TCS on weekends, to minimize TCS-induced side effects) is a newer avenue to consider in inflammatory dermatoses. The utility of nanoparticles incorporated with crisaborole to enhance drug penetration is another prospect that can be considered. Furthermore, the application of crisaborole in treating various inflammatory dermatoses in the pediatric population needs scrupulous evaluation. Last but not the least, head-to-head comparative trials of crisaborole with TCIs and TCS are warranted to substantiate the exact position of crisaborole in the treatment algorithm of AD.

Conclusion

Crisaborole has shown to be a valuable topical agent for many dermatoses apart from AD. Due to its non-steroidal nature, it serves as a safe therapeutic option that can be continued for a longer duration. The only drawback is the high cost compared to other topical agents.

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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