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# Atopic Dermatitis in Skin of Colour Patients: A Clinically Practical Literature Review Summary

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## Introduction

The growing interest in understanding the nuances of dermatologic conditions across diverse ethnicities continues to gain momentum amongst practising dermatologists and residents. It is encouraging to see residency programs evolving to encompass a wider range of cases, both common and rare, from various ethnic backgrounds.

Atopic dermatitis is a common condition that every dermatologist encounters in their practice. However, its nuances in presentation amongst patients of varying skin tones can present significant challenges in diagnosis and management.

To gather the most up to date, clinically applicable knowledge in atopic dermatitis patients with skin of colour, a literature review of all systematic reviews published in the last 5 years on this topic was conducted. Three papers were

chosen: Napolitano et al.,<sup>1</sup> Adawi et al.,<sup>2</sup> and Gan et al.<sup>3</sup> The most clinically relevant aspects of these papers are summarized below.

## Immunologic Profiles

Interleukin (IL)-13 has been identified as a key interleukin at play in atopic dermatitis. Interestingly, IL-13 expression has been found to be comparable across ethnic groups. However, nuances do exist in levels of expression of other interleukins implicated in atopic dermatitis.

## Pediatrics

Pediatric patients show greater epidermal hyperplasia and cellular infiltration compared with adults. They also express higher levels of T-helper (Th)17, Th9/IL-9, IL-33, innate markers, IL-31, and IL-33 than adults. This increase is thought to be responsible for the phenotypic similarities to psoriasis observed in pediatric patients.<sup>1</sup>

## African American

Studies have shown that the skin of African American patients has lower levels of ceramide, a lower pH in the stratum corneum, and higher trans-epidermal water loss compared with other ethnicities.<sup>2</sup> This results in increased xerosis. African American patients also tend to have increased Th2 and Th22 pathways.

## Asian

Chinese patients have been shown to have higher levels of Th2, Th17/IL-23, and Th22 in small studies.<sup>1</sup> The increased involvement of the latter 2 pathways may explain why Chinese patients can occasionally present with a psoriasiform thickening, as highlighted in the morphology section.

## Morphology

In general, patients with skin of colour may exhibit other morphologic features beyond the classic morphology described in the Hanifin and Rajka criteria. For example, primary morphological features such as lichenification, greater papular involvement, perifollicular accentuation, hyperkeratosis, xerosis, and annular lesions are more likely to be observed.<sup>3</sup> Secondary skin changes that are more likely to be observed include infraorbital fold dyspigmentation, palmar hyperlinearity, and Dennie-Morgan lines.<sup>3</sup>

Unfortunately, patients with skin of colour are more likely to present with greater disease severity in both pediatric and adult populations. This is a result of delays in diagnosis due to unfamiliarity with their unique morphology, and health care disparities.<sup>2</sup> Adawi et al. proposed adding these unique morphologic features to the Hanifin and Rajka criteria when assessing a patient with skin of colour to enhance diagnostic accuracy (**Table 1**).

Another attribute that may contribute to misdiagnosis and delays in treatment is the underappreciation of erythema, leading to an under-representation of severity. Gan et al. suggested that patient symptoms, such as itch intensity, could be used as markers of disease and treatment response in conjunction with the Eczema Area and Severity Index (EASI) scores.

Another study suggested that increasing erythema scores on the EASI scoring system by one level in skin of colour patients may help account for the under-representation of easily appreciable erythema to the eye.<sup>3</sup>

## African American

African American patients tend to have involvement of the extensor and truncal surfaces,<sup>3</sup> and occasionally, lesions can appear lichenoid (**Figure 1**). Studies have also shown that these patients experience more severe pruritus and prurigo nodularis compared with White ethnicities.<sup>3</sup>

## Asian

White dermatographism can be seen more commonly in Asian patients. Occasionally, the diagnosis may be unclear because the eruption in some Asian patients can appear more psoriasiform in nature. In these cases, if a skin biopsy shows features of both spongiotic and psoriasiform dermatitis, it is critical to establish the other major criteria of atopic dermatitis to confirm the correct diagnosis and treatment.

## Treatments Supported by Data from Published Studies Focusing on Skin of Colour Patients

Regrettably, non-White ethnic groups have historically been under-represented in clinical trials. Gan et al. comprehensively reviewed the literature for studies focusing specifically on treatments for patients with atopic dermatitis who have skin of colour. The treatments included topical, phototherapy, oral, biologic, Janus kinase (JAK) inhibitors, and emollients. The findings are summarized below by category.

## Topical

### Topical Steroids and Calcineurin Inhibitors

Unfortunately, no data exists comparing response rates to topical steroids in atopic dermatitis across different ethnic groups.<sup>3</sup> However, sub-analyses of pivotal trials have shown that pimecrolimus 1% cream and crisaborole ointment showed similar efficacy among all racial groups.<sup>3</sup> Pooled data on tacrolimus

| Major Criteria<br>(≥3 required)                                                                                                                                                                                                                                                                                                                                                                                                                                             | Minor Criteria<br>(≥3 required)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Pruritus</li> <li>• Typical morphology and distribution</li> <li>• Flexural lichenification</li> <li>• <b>Extensor papular involvement, lichenification or psoriasiform thickening of skin in skin of colour patients</b></li> <li>• Extensor eruptions in infants and children</li> <li>• Chronic or chronically relapsing dermatitis</li> <li>• Personal or family history of atopy (asthma, allergic rhinitis or AD)</li> </ul> | <ul style="list-style-type: none"> <li>• <b>Dyspigmentation (post-inflammatory hypopigmentation and hyperpigmentation)</b></li> <li>• <b>Psoriasiform scaling</b></li> <li>• <b>Perifollicular accentuation</b></li> <li>• <b>Secondary papular involvement/prurigo nodule formation</b></li> <li>• Xerosis</li> <li>• Ichthyosis, palmar hyper linearity, or keratosis pilaris</li> <li>• Immediate (type I) skin test reactivity</li> <li>• Raised serum IgE</li> <li>• Early age of onset</li> <li>• Tendency toward cutaneous infections (especially <i>S. aureus</i> and herpes simplex) or impaired cell-mediated immunity</li> <li>• Tendency toward non-specific hand or food dermatitis</li> <li>• Nipple eczema</li> <li>• Cheilitis</li> <li>• Recurrent conjunctivitis</li> <li>• Dennis-Morgan infraorbital fold</li> <li>• Keratoconus</li> <li>• Anterior subscapular cataracts</li> <li>• Orbital darkening</li> <li>• Facial pallor or facial erythema</li> <li>• Pityriasis alba</li> <li>• Anterior neck folders</li> <li>• Itch when sweating</li> <li>• Intolerance to wool and lipid solvents</li> <li>• Food intolerance</li> <li>• Course influenced by environment or emotional factors</li> <li>• White demographism or delayed blanch</li> </ul> |

**Table 1.** Proposed Hanifin and Rajka criteria for Atopic Dermatitis, adjusted for characteristics more frequently seen in atopic dermatitis patients; *adapted from Adawi W., et al., 2023.*

showed comparable efficacy in Asian patients to studies conducted in Western countries.<sup>3</sup>

### **Ruxolitinib Cream**

In the pivotal Phase III study, ruxolitinib 1.5% cream, a JAK 1 and 2 selective topical approved in the United States for

mild-moderate atopic dermatitis, significantly improved itch, sleep, and quality of life across various races and ethnicities.<sup>3</sup> In addition, it provided greater itch reduction than topical triamcinolone, while not having the associated risk of hypopigmentation.<sup>3</sup>



**Figure 1.** Lichen planus-like morphology in an atopic dermatitis patient; courtesy of Gan et al., 2023.

Among the patients in the study with Black ethnicity, 38.1% of those using ruxolitinib cream achieved a >2 Investigator's Global Assessment (IGA) score versus 11.5% of those using vehicle cream.<sup>3</sup> For patients with White ethnicity, 57.3% of those using ruxolitinib cream achieved a >2 IGA score versus 12.3% of those using vehicle cream.<sup>3</sup> Among Asian patients, 56.3% of those using ruxolitinib cream achieved a >2 IGA score versus 5% of those using vehicle cream.<sup>3</sup>

In the entire study, 29% of the patients were of Black ethnicity, and 8% were of Asian ethnicity, providing a greater representation of

non-Caucasian ethnicities than historically seen in prior atopic dermatitis studies.<sup>3</sup>

### **Roflumilast Cream**

Roflumilast 0.15% cream, is a topical phosphodiesterase 4 (PDE4) inhibitor that is approved in Canada for atopic dermatitis.<sup>3</sup> IgA 0 or 1 score was achieved in roflumilast-treated patients in INTEGUMENT-1 at week 4 compared with placebo, regardless of race (32.3% in White patients vs. 13.3%, 25.8% vs. 11.5% in Black patients, 33.7% vs. 21.8% in Asian patients, 33.2% vs. 13.7% in "Other" patients).

### **Phototherapy**

Patients with skin of colour often have richer pigmentation; therefore, higher treatment doses are often needed. However, there is a corresponding greater risk of dyspigmentation and developing melasma. Thus, it is important to inform patients about these risks prior to initiating phototherapy, since inducing a new dermatologic condition is undesirable.<sup>3</sup>

### **Oral**

#### **Cyclosporine**

The bioavailability of cyclosporine (CsA) in patients of Black ethnicity is 20–50% lower than that in those of White ethnicity. This difference is due to more frequent expression of cytochrome P450 (CYP) 3A5 and the resultant increased metabolism of CsA.<sup>3</sup> Thus, higher doses may be required to achieve a therapeutic effect.<sup>3</sup> Of note, Black ethnic groups demonstrate the highest rates of gingival hypertrophy and hypertrichosis while taking CsA.<sup>3</sup> This would be a worthy point to mention during counselling.

#### **Azathioprine**

Thiopurine methyltransferase (TMPT) is the key enzyme involved in the metabolism of azathioprine (AZA). TMPT activity is lower in patients of Black ethnicity, which pre-disposes them to higher than intended drug levels within the body.<sup>3</sup> Gene mutations that impair TMPT function differ among Black (TMPT\*3C, \*8), East Asian (\*3C) and White (\*3A) ethnicities.<sup>3</sup> This variation is important to consider when determining which

target genes to test for in a patient's specific ethnicity before starting AZA.<sup>3</sup> For those with heterozygous mutations, treatment should start at 30–70% of the target dose. Those with homozygous mutations should consider other agents, a 10-fold reduction in daily dosing, or dosing 3 times a week.<sup>3</sup>

### **Methotrexate**

There is an ethnic predisposition for methotrexate-induced alopecia in people of Black ethnicity, possibly due to single-nucleotide polymorphisms in the methotrexate cellular pathway.<sup>3</sup>

### **Mycophenolate Mofetil**

There are no studies with mycophenolate mofetil that compare pharmacokinetics amongst different ethnicities.<sup>3</sup>

### **Dapsone**

Those with glucose 6 phosphate dehydrogenase (G6PD) deficiency, which is more common in Black and Asian ethnicities, have an increased risk of hemolytic anemia when treated with dapsone.<sup>3</sup>

## **Biologics**

### **Dupilumab**

In the pivotal Phase III studies SOLO-1 and SOLO-2, there were comparable efficacy and safety profiles for dupilumab treatment in subgroup analyses amongst Asian, Black, Indian, and White ethnicities, although Black ethnicities were under-represented.<sup>3</sup> A higher baseline risk for allergic conjunctivitis was also observed in Asian ethnicities.<sup>3</sup>

### **Tralokinumab**

The pivotal Phase III ECZTRA 1 and 2 studies on tralokinumab treatment did not include subgroup analyses between ethnic groups. However, beyond these studies no disparities in clinical response were reported across ethnic groups.<sup>3</sup>

### **Lebrikizumab**

No direct comparison of efficacy between ethnicities was performed in the pivotal Phase III ADvocate 1 & 2 studies of lebrikizumab.<sup>3</sup> However, ADmirable, a Phase IIIb open label study dedicated to atopic dermatitis patients with skin of colour (Skin Phototype IV, V and VI) showed that 69.2% and 44.9% of patients were able to achieve EASI 75 AND 90 at Week 16, respectively. There were no new safety signals in this study.<sup>4</sup>

### **JAK Inhibitors**

In general, Phase III studies on JAK inhibitors for atopic dermatitis lacked ethnic subgroup analyses.<sup>3</sup>

## **Upcoming Treatments**

### **Tapinarof Cream**

Tapinarof is currently approved for atopic dermatitis in the United States, and has recently been approved in Canada for use in psoriasis, but has not yet received approval for use in atopic dermatitis.

### **Nemolizumab (IL-31)**

Phase III studies on nemolizumab (IL-31) conducted in Japan and Western countries show similar reductions in EASI and pruritus, although each trial used different scoring systems for pruritus.<sup>3</sup>

## **Failed Trials**

### **IL-12/23**

Despite the increased IL-23 signalling in Asian patients with atopic dermatitis, as mentioned in the immunologic profile section, a randomized study of 79 Japanese patients with atopic dermatitis demonstrated no meaningful efficacy for ustekinumab.<sup>3</sup> Data supporting ustekinumab efficacy in atopic dermatitis is scant regardless of skin type.<sup>3</sup>

### **IL-17**

Secukinumab did not significantly reduce epidermal thickness of lesional skin in 41 patients of Asian ethnicity, despite the increased IL-17

signalling identified in Asian patients, as mentioned in the immunologic profile section.<sup>3</sup>

## IL-22

Fezakinumab, an IL-22 monoclonal antibody inhibitor, showed no significant difference in efficacy despite biopsy-proven increases in Th22 predominance among study patients.<sup>3</sup>

In general, these failed trials may indicate that immunologic signalling pathways in atopic dermatitis are more complex than a single target of blockade. Further studies are required to elucidate its clinical significance beyond morphologic nuances between ethnicities.<sup>3</sup>

## Emollients

Although urea, glycerine, and propylene glycol are emollients, they can be irritating and worsen skin sensitivity, especially in Asian patients, who were found to have the most sensitive skin according to a skin sensitivity test.<sup>3</sup> Squalene was found to be less irritating.<sup>3</sup>

## Conclusion

In summary, the current understanding of atopic dermatitis and its nuances between ethnicities remains incomplete. However, this article highlights clinically helpful and relevant differences in morphologic appearance and pharmacologic metabolism that every dermatologist can add to their arsenal in tailoring their treatment for atopic dermatitis in patients with skin of colour. With increased representation of patients with skin of colour in future atopic dermatitis studies, our understanding can continue to expand.

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## Financial Disclosures

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