Review Article

Exploring Topical Abrocitinib as A Targeted Therapy for Atopic Dermatitis

Sincy Sebastian*, Anit Joji George, Maria Shaji, Muhammed Afeed
Caritas College of Pharmacy, Ettumanoor, Kerala, India.
***Corresponding author's E-mail:** sincysebastian2002@gmail.com

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ABSTRACT

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disorder with increasing prevalence globally, imposing a significant burden on patients and healthcare systems. Current treatment modalities include topical corticosteroids, calcineurin inhibitors, and systemic agents; however, these often fall short in addressing unmet therapeutic needs such as localized efficacy, safety, and patient adherence. The advent of Janus kinase (JAK) inhibitors has introduced a novel mechanism targeting the inflammatory pathways central to AD pathophysiology. Among these, abrocitinib, an oral JAK1-selective inhibitor, has demonstrated efficacy in moderate-to-severe AD but lacks a topical formulation optimized for localized action and reduced systemic exposure. This review delves into the epidemiology and pathophysiology of AD, evaluates the role of JAK inhibitors, and highlights challenges and innovations in developing targeted therapies. It further examines clinical evidence supporting abrocitinib's efficacy, its dosage, administration, and regulatory status while exploring the potential of nanoliposomal delivery systems to enhance topical formulations. By addressing gaps in AD management, this review underscores the need for innovative therapeutic strategies to improve patient outcomes.

Keywords: Atopic Dermatitis, Abrocitinib, Janus kinase pathway, JAK Inhibitors, Topical Therapy.

INTRODUCTION

A selective small molecule Janus kinase (JAK)-1 inhibitor called abrocitinib (PF-04965842) is being developed to treat moderate-to-severe atopic dermatitis at daily dosages of 200 and 100 mg.[1] Abrocitinib selectively inhibits cytokines that signal through JAK1-dependent pairs [i.e., JAK1/JAK2, JAK1/JAK3, and JAK1/tyrosine kinase (TYK) 2]. This includes cytokines such as interleukin (IL)-4, IL-13, and others like IL-31, IL-22, and thymic stromal lymphopoietin involved in the pathogenesis of atopic dermatitis and pruritus.[2] Non-JAK1 pairs, such as JAK2/JAK2 inhibition, are spared, reducing the risk of anemia and neutropenia.[3]

For adults and children aged 12 and up who are unable to use other medications for their condition or whose eczema has not responded to other treatments, abrocitinib is used to treat moderate to severe eczema (atopic dermatitis), a skin disease that causes the skin to be dry and itchy and occasionally develop red, scaly rashes. Abrocitinib belongs to a group of drugs known as Janus kinase (JAK) inhibitors. It functions by reducing the immune system's activity.[4]

Dermatologists are investigating new therapy alternatives called Janus kinase (JAK) inhibitors.[5-7] JAK inhibitors exhibit wide immune-suppressive effects because their action affects the signaling of several cytokines, as opposed to their monoclonal antibody-based rivals' more targeted inhibition.[8] Numerous proinflammatory pathways converge on the intracellular signaling system known as the JAK-signal transducers and activators of transcription (JAK-STAT) pathway, which is the target of JAK inhibitors. The pathogenesis of several immune-mediated inflammatory skin conditions, such as vitiligo, psoriasis, alopecia areata, and atopic dermatitis (AD), is significantly influenced by the JAK-STAT pathway.[9]

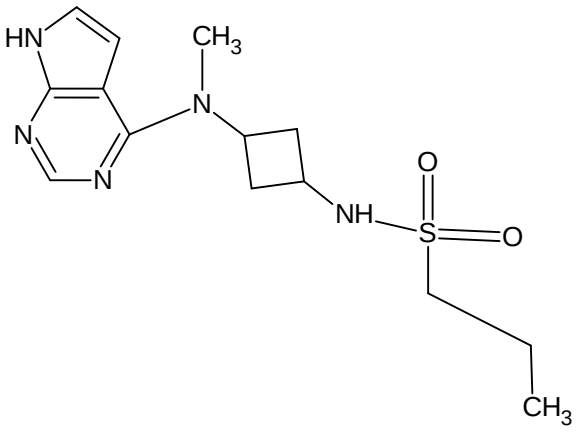
Children and adults are at greater risk for atopic dermatitis (AD), a chronic inflammatory skin disorder caused by the immune system. It might be persistent or relapsing-resolving with frequent flare-ups, and it is typified by extremely itchy and inflammatory eczematous lesions.[10] Pfizer recently created the tiny drug abrocitinib (PF-04965842), which is being researched to treat AD.[11] The JAK1 protein, which is thought to alter cytokines in the pathogenesis of AD, is selectively inhibited by oral abrocitinib. Abrocitinib's safety and effectiveness in treating AD have been evaluated in some clinical trials (phase I, II, and III). [12–18]With an estimated 10–20% prevalence in developed nations, AD prevalence has dramatically increased during the last 30 years. [19]

Although AD can appear at any age, in over 60% of cases it begins in early infancy [20]. There isn't a single known pathophysiological reason for atopic dermatitis.[21]There are some subtypes of AD, such as hand and foot, intrinsic, extrinsic, and pediatric-onset.[22] The molecular makeup and triggering factors of these subgroups vary.[23] For instance, only 20–50% of patients had high IgE levels, and only a small percentage of AD patients with European ancestry have been shown to have loss-of-function mutations in the filaggrin (FLG) gene[24]Nonetheless, a cycle of T cell-mediated skin inflammation and skin barrier breakdown characterizes all AD subtypes. [25]

Abrocitinib has a black box warning for increased risk of major adverse cardiac events (MACE), thrombosis, death, and serious bacterial, fungal, viral, and opportunistic infections. [26] Using information from one phase IIb trial, four phase-III clinical studies (MONO-1, MONO-2, COMPARE, REGIMEN), and one long-term extension study (EXTEND), a pooled analysis assessed the short- and long-term safety of abrocitinib. Participants with moderate-to-severe atopic

dermatitis who were at least 12 years old (MONO-1, MONO-2, REGIMEN, and EXTEND) and at least 18 years old (phase IIb and COMPARE) were included in these trials. These studies' data were divided into two cohorts: one that was abrocitinib- controlled (n = 2856) and the other that was placebo-controlled (n = 1540). Patients on abrocitinib 100 mg (n = 608), abrocitinib 200 mg (n = 590), or placebo (n = 342) made up the placebo-controlled cohort, where*as patients on abrocitinib 100 mg (n = 885) and abrocitinib 200 mg (n = 1971) made up the all abrocitinib group.[17]

MOLECULAR STRUCTURE



CURRENT FORMULATIONS OF ABROCITINIB FOR ATOPIC DERMATITIS

Abrocitinib tablets: These come in a range of strengths, usually 100 and 200 mg, so the dosage can be changed according to the patient's requirements and reaction. Dosage Schedule: Typically, a starting dose of 200 mg once daily is advised; however, depending on effectiveness and tolerability, this may be lowered to 100 mg. Cibinqo is one of the common brand names.[27]

The following dosage formulations of Cibinqo are available for oral use:

50 mg, 100 mg, and 200 mg oral pills are available.

Cibinqo should be kept at room temperature, between 68°F and 77°F (20°C and 25°C), in its original packing. For a brief period, as during transportation, it can be subjected to temperatures ranging from 59 to 86 degrees Fahrenheit (15 to 30 degrees Celsius). Keep out in a dry, cool area. [28]

SIDE EFFECTS OF ABROCITINIB

Common mild side effects of abrocitinib (Cibinqo) include infections of the nose, throat, skin, or bladder; flu-like symptoms (sore throat, nausea, vomiting, and stomach discomfort); headache; fatigue; high creatine phosphokinase; low blood platelet counts; and acne. A higher chance of serious infections like shingles or tuberculosis, which manifest as coughing, fever, dyspnea, or excruciating rashes, is one of the serious side effects. Breathing problems, facial or throat swelling, a severe rash, lightheadedness, or a racing heart are some of the symptoms of allergic responses. Shortness of breath, chest pain, or swollen or red legs are symptoms of blood clots (DVT/PE).

Additionally, there is an increased risk of heart attack or stroke, especially in people who already have heart disease, which is manifested by symptoms including weakness, slurred speech, chest pain, or an irregular pulse. Symptoms of blood abnormalities, such as low white blood cell or platelet counts, can include bruises, shortness of breath, frequent infections, and pale complexion. Finally, smoking increases the risk of developing malignancies including skin, lung, or lymphoma. [29]

EPIDEMIOLOGY AND PREVALENCE OF ATOPIC DERMATITIS

The pediatric population has been the focus of AD epidemiology.[30] The demographic, and illness definition technique may all have an impact on the diversity in the prevalence of AD in adults, according to the limited data available. Adult AD point prevalence rates ranged from 0.3% (Switzerland) to 6.2% (Estonia) according to the European Community Respiratory Health Survey (ECRHS) study (N = 8206), which was based on self-diagnosis in the adult population of 11 European nations and the US. [31] According to the population assessed and the definition applied, reported point prevalence rates in some US studies ranged from 3.2% to 10.7%. [32–34] With 1-year and lifetime prevalence rates of 3.0% and 3.3%, respectively, the estimated point prevalence of adult AD in the Japanese population was 2.9%. [35]

The epidemiologic statistics mentioned above point to clear knowledge gaps regarding the prevalence of AD in adults. These gaps have been caused by some issues, such as inconsistent application of diagnostic criteria to epidemiologic evaluation, the absence of a commonly used metric for determining severity, and inadequate sample representativeness that would have allowed for generalizability to the larger population (for example, only one city represented the US sample in the ECRHS study). [31]

This study's main goal was to close these gaps by supplying worldwide data on the prevalence of AD in representative adult samples from various nations utilizing uniform diagnostic criteria and constantly utilizing tried-and-true techniques from earlier research. Using verified patient-reported outcomes, a secondary goal was to allow for a robust and comparative calculation of AD prevalence by disease severity in each nation. [36]

Globally, the 12-month prevalence of atopic dermatitis (AD) varies from 2.1% in Japan to 8.1% in Italy; geographical variations are seen within and between nations. [37] Excluding the US and the UK, the prevalence of AD was higher in women overall and peaked in younger age groups before declining with age. Less than 10% of cases were diagnosed by a physician; Spain (17.6%), Italy (12.4%), and the US (10.6%) had the highest percentages. Asthma prevalence was notably lowest in Japan (10.5%) and highest in Spain (26%), with common symptoms like dry skin and itching varying by country.[38]

OCCURRENCE OF JAK INHIBITORS ON SKIN

Krebs and Fischer's work from 1966, which demonstrated the critical role of phosphorylation as a process of cell physiology, established the significance of protein kinases and their vital enzymatic activity [39]. Transferring phosphate groups from adenosine triphosphate (ATP) or guanosine triphosphate (GTP) to the hydroxyl groups of their protein substrates is the main job of protein kinases [40]. For cytokine receptors, which do not have intrinsic enzymatic activity, this mechanism is equally crucial. In general, an inflammatory signal is started when cytokines attach to their receptors. Numerous cytokines interact with so-called type I and II cytokine receptors. These include interleukins (IL) like IL-2, IL-6, IL-12, IL-21, IL-22, and IL-23, as well as interferons like IFN-γ.

Due to their lack of inherent enzyme activity, both of these receptor types heavily depend on JAKs for signal transduction [41].

A family of molecules known as the Janus kinase (JAK) and signal transducer/activator of transcription (STAT) signaling pathway are connected to the intracellular domains of receptors for different growth factors and cytokines, and they mediate their signaling to the nucleus. [42]

The JAK-STAT pathway is part of an intricate system of evolutionarily conserved protein kinases where extracellular mediators regulate the expression of particular genes involved in some cell processes, including differentiation, apoptosis, hematopoiesis, mitosis, immune system development (both innate and adaptive), and exocrine gland activity. It also takes part in how cells react to assaults such as oxidative damage, hyperosmolar stress, endotoxin stimulation, hypoxia, and UV radiation.[43]

JAKi reduces systemic side effects and pharmacological interactions in topical preparations by not raising serum drug levels. Additionally, the epidermis and higher dermis have large amounts of these. To lessen the possibility of systemic effects, it is advised to apply a thin layer, not to cover more than 20% of the skin, and to stop using it for an extended period.[44]

In dermatology, Janus kinase (JAK) inhibitors have become a game-changing class of drugs that have a big influence on the treatment of some inflammatory and autoimmune skin disorders, such as vitiligo, psoriasis, alopecia areata, and atopic dermatitis. [45]The JAK-STAT signaling pathways that mediate inflammation are disrupted by these medicines, which quickly improves symptoms including itching and skin sores.[46]

The effectiveness of JAK inhibitors in treating these difficult illnesses is demonstrated by the FDA's approval of several of them, such as deucravacitinib for psoriasis and ruxolitinib for vitiligo and atopic dermatitis. [47]JAK inhibitor use is not risk-free, though; research has shown that acne is a common side effect, especially when using larger dosages and longer treatment periods. Patient adherence to treatment may be impacted by this side effect. [48]All things considered, even though JAK inhibitors provide many patients with dermatological conditions with substantial therapeutic benefits, clinical practice must carefully evaluate any possible negative consequences. [49]

UNMET NEEDS IN THE CURRENT TREATMENT OF ATOPIC DERMATITIS

Despite being helpful for many patients, the current therapies for atopic dermatitis (AD) include serious side effects that reduce their efficacy and patient compliance. Frequently used as the first-line treatment, topical corticosteroids can cause striae, telangiectasia, and skin thinning (atrophy), especially if used improperly or over an extended period. [50]When it comes to long-term care for pediatric patients or sensitive areas like the face, these consequences can be particularly problematic. Another topical alternative that is less likely to result in skin atrophy is calcineurin inhibitors, which can induce burning sensations, skin irritation, and, in rare instances, an increased risk of cancer with prolonged usage. This raises concerns for both patients and clinicians. [51]

Oral corticosteroids and immunosuppressants like cyclosporine, methotrexate, or azathioprine are examples of systemic therapies for moderate-to-severe AD that frequently offer quick symptom relief but come with significant hazards. Systemic side effects include weight gain, osteoporosis, hypertension, and adrenal suppression can result from long-term usage of oral corticosteroids. Despite their ability to reduce inflammation, immunosuppressants are linked to organ toxicity, such as hepatotoxicity (with methotrexate) and nephrotoxicity (with cyclosporine), as well as an increased risk of infections and cancers since they suppress the immune system. Their long-term usage is limited by these side effects, which also call for careful monitoring. [52]

By focusing on particular immunological mechanisms implicated in AD, biological treatments like dupilumab have completely changed the way the disease is treated. However, many patients find it difficult to afford them, and the requirement for frequent injections can be frightening and uncomfortable.[53] Furthermore, even though biologics are usually well tolerated, some patients may decide not to continue treatment because of side effects such as conjunctivitis, injection site reactions, and uncommon allergic reactions. [54]

In addition to these difficulties, a lot of patients have frequent flare-ups or insufficient symptom alleviation, which calls for several modifications to treatment plans. The necessity for alternative therapeutic approaches that target the underlying causes of AD while reducing systemic exposure, side effects, and patient burden is highlighted by the combination of these restrictions.

To fulfill the unmet demands of managing AD, a topical formulation that may administer focused, localized therapy with improved efficacy and safety could be a major improvement.[55]Several unmet requirements persist despite advancements in the treatment of atopic dermatitis (AD),

underscoring the need for innovative therapeutic approaches. For moderate-to-severe cases, current topical treatments like calcineurin inhibitors and corticosteroids sometimes don't work for long and have unfavorable side effects such as skin atrophy, irritation, and even systemic absorption.[56]Options including corticosteroids, cyclosporines, and biologics provide some advantages for people in need of systemic therapy, but they are severely limited by issues with accessibility, toxicity, and expense.Biologics, such as dupilumab, for example, are costly, necessitate frequent injections, and do not alleviate all symptoms, leaving some patients with unresolved skin lesions or itching. [57]

Given the variability of AD in terms of triggers, severity, and responsiveness to treatment, there is also a dearth of customized medicines that address the needs of each patient. Due to the chronic, relapsing nature of AD, frequent relapses, and insufficient symptom control, many patients feel frustrated. Furthermore, there is still a lack of long-term safety data for more recent medications, which worries both patients and doctors. [58]

These gaps are exacerbated by practical issues, such as the stigma attached to visible symptoms and treatments, the frequency of applications, or disruptions in lifestyle that make it difficult to follow treatment plans. Therefore, the creation of safer, more efficient, and more reasonably priced treatments that offer long-term disease control, lower systemic risks, and enhance quality of life is one of the main unmet needs in AD. These crucial gaps could be filled by innovative formulations that improve localized medication delivery, lessen systemic exposure, and treat the underlying immunological dysregulation in AD. [59]

PATHOPHYSIOLOGY OF ATOPIC DERMATITIS

There is significant phenotypic variation and a complex etiology in AD.[60] Important proteins involved in epidermal function include keratins, transglutaminases, intercellular proteins, and filaggrin (FLG). These proteins' flaws make it easier for allergens and microorganisms to enter the skin. [61]Skin barrier dysfunction, frequently brought on by mutations in the filaggrin gene, is a key component of AD. This impairment of the skin's natural barrier increases transepidermal water loss and renders the skin more susceptible to allergens, irritants, and microorganisms. Dry skin and heightened vulnerability to pathogen colonization—particularly by Staphylococcus aureus, which releases toxins that function as superantigens and exacerbate immune responses—are the results of this compromised barrier. [62]An excessive type 2 helper T cell (Th2) response, which releases cytokines like IL-4, IL-13, and IL-31, is indicative of immune dysregulation in AD.

These cytokines cause itching and inflammation, and in long-term conditions, other immune pathways (Th1, Th17, Th22) support persistent inflammation and lichenification, or thickening of the skin. [63] Many people with AD have elevated IgE levels, which is indicative of heightened susceptibility to common environmental allergens, such as dust mites and specific foods. Scratching makes the cycle worse by weakening the skin barrier and causing more inflammation and itching.[64] AD symptoms can be triggered and exacerbated by environmental variables, including stress, climate change, and exposure to irritants. These elements work together to produce a vicious cycle whereby immune activation, itching, and degradation of the skin barrier result in persistent inflammation and the maintenance of AD symptoms.[65]

ABROCITINIB MECHANISM OF ACTION AND EFFICACY IN ATOPIC DERMATITIS

Numerous cytochrome P (CYP) enzymes, including as CYP2C19 (~53%), CYP3A4 (~11%), CYP2C9 (~30%), and CYP2B6 (~6%), are important in the metabolism of abrocitinib. Two active polar mono-hydroxylated metabolites, M1 and M2, were produced by the main circulating chemical, abrocitinib, in a recent investigation.[66]The activity of metabolite M1 was lower than that of abrocitinib, whereas that of metabolite M2 is similar to that of the parent.[67]Abrocitinib has a pharmacologic impact because the unbound parent molecule (~60%), M2 (~30%), and M1 (~10%) are exposed in the systemic circulation.[68]

With low immunogenicity and strong oral bioavailability, selective JAK1 inhibitors appear to be safe and effective for treating AD, overcoming some of the drawbacks of biological medications. Among other things, abrocitinib may alter the way we manage patients with moderate to severe AD. [69] It is far more effective than a placebo and appears to be on par with or even better than dupilumab, a monoclonal antibody that is frequently used in individuals with moderate-to-severe AD.[70] Additionally, abrocitinib initially reduced pruritus beginning two days into the course of treatment. Before the condition is clinically under control, this quick effect might make patients more likely to stick with their treatment. There were very few patient dropouts during clinical studies, indicating that the safety and tolerability profile was satisfactory. [71] However, long-term real-life data and head-to-head studies for other JAK inhibitors and biologic medicines will be necessary to assess its most appropriate function in treating AD. [72]

CHALLENGES AND INNOVATIONS IN ATOPIC DERMATITIS

An ideal animal model that fully replicates the histology and immunophenotypic characteristics of AD as observed in people is required. [73] Although numerous genetic and immunological animal models have already been developed, neither model fully captures the limitations of the disease. [74] Additionally, due to the disease's heterogenicity and the fact that current models more closely resemble "allergic dermatitis" than AD, the author proposes setting minimum standards for mouse models to be representative of AD in humans and looks at how each of the current models satisfies some requirements while failing to meet others. [75]There are three well-researched mouse models: transgenic mice, spontaneous mutation, and epicutaneous sensitization. [76]

CLINICAL EVIDENCE THAT ABROCITINIB IS USED IN ATOPIC DERMATITIS

Based on strong clinical evidence, the oral Janus kinase (JAK) 1-selective inhibitor abrocitinib has become a promising treatment for moderate-to-severe atopic dermatitis (AD). [77]It reduces symptoms including itching, erythema, and skin lesions by specifically blocking JAK1-mediated signaling pathways that are involved in the hyperactive immune responses that cause inflammation in AD. Its effectiveness and safety have been proven in several pivotal clinical trials, including JADE MONO-1, JADE MONO-2, and JADE COMPARE.[78]

Abrocitinib continuously beat a placebo in several trials, resulting in notable improvements in important clinical outcomes. According to the Eczema Area and Severity Index (EASI-75), patients receiving abrocitinib demonstrated significant improvements in disease severity, with improvements of 75% or more from baseline.[79]Furthermore, a larger percentage of patients received an Investigator's Global Assessment (IGA) grade of "clear" or "almost clear." Notably, abrocitinib quickly reduced the severe itching linked to AD; within days of beginning treatment, several patients reported improvements on the Peak Pruritus Numerical Rating Scale (PP-NRS).[80]

The JADE COMPARE trial further established abrocitinib as a viable substitute for the popular biologic treatment dupilumab. Abrocitinib showed comparable or better efficacy in head-to-head comparisons, especially when it came to its quicker start of action, which is advantageous for patients who need treatment right away. Since pruritus significantly impairs the quality of life in AD patients by interfering with sleep and everyday activities, this quick reduction in itching is clinically significant.[81]

Although abrocitinib has been well tolerated in clinical settings, it is nevertheless important to keep an eye on its adverse effect profile. Mild nausea, headaches, and temporary test abnormalities such as elevated creatine phosphokinase and decreased platelet counts are common side effects. For the majority of patients, these adverse effects were tolerable and did not outweigh the advantages. [82]

According to the clinical data, abrocitinib is a practical and efficient oral treatment for AD, especially for patients who don't react well to topical therapies or who would rather not use injectable biologics like dupilumab. [83] Abrocitinib is positioned as a useful addition to the therapeutic arsenal for controlling moderate-to-severe AD due to its capacity to quickly manage symptoms, particularly pruritus. [84]

DOSAGE, ADMINISTRATION AND REGULATORY APPROVAL OF ABROCITINIB

Patients with moderate-to-severe atopic dermatitis (AD) who are suitable for systemic therapy can be treated with the oral Janus kinase (JAK) 1-selective inhibitor abrocitinib.[85] It comes in tablet form, and patients who need more thorough symptom control can choose to take 200 mg once daily in addition to the regular 100 mg. Certain groups, such as individuals with hepatic or renal impairment or those who are more likely to have side effects, may require dose modifications.[86]When taken orally, either with or without food, abrocitinib provides a practical substitute for injectable biologics for individuals who would rather take their medication orally. Based on data from pivotal trials including JADE MONO-1, JADE MONO-2, and JADE COMPARE, the medication was approved by key health agencies, including the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), and the Japanese Ministry of Health, Labor, and Welfare. [87] These studies showed that it was effective in lessening pruritus and lowering the severity of the condition while keeping a controllable safety profile. However, cautious monitoring is advised during treatment due to possible adverse effects, such as headaches, nausea, and changes in laboratory markers like platelet counts. [88]

OTHER ATOPIC DERMATITIS TREATMENT

Based on strong clinical evidence, the oral Janus kinase (JAK) 1-selective inhibitor abrocitinib has become a promising treatment for moderate-to-severe atopic dermatitis (AD).[89]It reduces symptoms including itching, erythema, and skin lesions by specifically blocking JAK1-mediated signaling pathways that are involved in the hyperactive immune responses that cause inflammation in AD. Its effectiveness and safety have been proven in several pivotal clinical trials, including as JADE MONO-1, JADE MONO-2, and JADE COMPARE. [90]

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CONCLUSION

Abrocitinib, a selective JAK1 inhibitor, has emerged as a promising treatment for moderate-to-severe atopic dermatitis, offering a targeted approach to managing this chronic and debilitating condition. By selectively inhibiting JAK1-dependent cytokines, abrocitinib addresses key mediators of inflammation and pruritus while minimizing the risks associated with broader immunosuppression. Clinical trials have demonstrated its efficacy and safety across diverse patient populations, highlighting its potential to improve disease outcomes and quality of life for patients who fail to respond to traditional therapies.

Despite its therapeutic promise, the black box warnings for severe adverse effects, including infections, malignancies, and thrombotic events, underscore the need for careful patient selection and monitoring during treatment. The increasing prevalence and heterogeneity of atopic dermatitis emphasize the importance of individualized treatment strategies, with abrocitinib providing an important option in the evolving landscape of JAK inhibitors.

Further research is needed to refine its long-term safety profile, explore its role in combination therapies, and expand its use across different AD subtypes. As our understanding of atopic dermatitis and JAK-STAT signaling deepens, abrocitinib may pave the way for more precise and effective management of this complex disease.

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