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Review

The Use of JAK Inhibitors in AD Affecting Difficult-to-Treat Areas: Lessons from Real-Life

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Abstract

Background: Difficult-to-treat anatomical areas in atopic dermatitis (AD), including the head and neck, hands, genital and intertriginous regions, are frequently associated with therapeutic refractoriness, persistent pruritus, and substantial functional and psychosocial burden. Real-world evidence (RWE) regarding the effectiveness of Janus kinase (JAK) inhibitors in these site-dominant phenotypes remains fragmented. This structured narrative review aimed to synthesize available RWE on abrocitinib, baricitinib, and upadacitinib in AD involving difficult-to-treat areas. **Methods:** A comprehensive search of PubMed, Ovid MEDLINE, Scopus, Embase, and the Cochrane Library was conducted up to 31 December 2025. Real-world observational studies reporting site-specific outcomes in patients with AD treated with JAK inhibitors were included. Primary randomized controlled trial efficacy analyses were excluded, while relevant post hoc regional analyses were considered. A total of 22 studies met eligibility criteria for qualitative synthesis. **Results:** Across heterogeneous real-world cohorts, JAK inhibitors demonstrated clinically meaningful improvement in difficult anatomical regions, particularly the head and neck and hands. Rapid pruritus reduction was a consistent and clinically relevant finding. Safety profiles were broadly aligned with clinical trial data. **Conclusions:** Real-world data support JAK inhibitors as effective options for anatomically complex AD phenotypes, warranting further standardized regional assessment.

Keywords: atopic dermatitis; difficult-to-treat areas; JAK inhibitors

Academic Editor: Giulia Ciccarese

Received: 17 February 2026
Revised: 14 April 2026
Accepted: 14 May 2026
Published: 4 June 2026

1. Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease characterized by intense pruritus, eczematous lesions, and skin barrier dysfunction [1]. Its prevalence is increasing worldwide, affecting up to 10% of adults in developed countries, and it is associated with a substantial burden on quality of life, particularly when visible or functionally sensitive anatomical sites are involved [2,3]. Although AD can affect the entire integument, certain anatomical areas commonly referred to as "difficult-to-treat areas" pose unique clinical and therapeutic challenges [4]. These include the head and neck, hands, feet, genital and intertriginous areas, as well as the periocular and perioral regions. The involvement of these sites is not only associated with greater disease severity and resistance to treatment, but also with disproportionate impacts on patients' psychosocial functioning,

stigmatization, sleep, daily activity, and emotional well-being [5,6]. From a pathophysiological standpoint, difficult-to-treat areas may display distinct clinical phenotypes, microbial colonization profiles, and local immune responses that contribute to chronicity or reduced therapeutic responsiveness [4]. For example, the head and neck area is frequently reported to be refractory to treatment and prone to paradoxical erythema, particularly under IL-4/13 blockade [7,8]. Similarly, hand eczema, due to its exposure to irritants and mechanical trauma, is often chronic and difficult to clear, leading to occupational impairment and increased rates of anxiety and depression [9]. Over the past decade, biologics such as dupilumab have revolutionized the treatment of moderate-to-severe AD [10,11]. However, real-world and post hoc trial analyses suggest that some patients do not achieve satisfactory clearance in difficult areas, and a proportion may discontinue treatment due to site-specific refractoriness or paradoxical effects [7,8,12]. Janus kinase (JAK) inhibitors represent a novel class of small molecules that interfere with intracellular signaling through the JAK–STAT pathway, a central mediator of cytokine signaling in AD pathogenesis. Upon cytokine binding to their receptors, associated JAK proteins (JAK1, JAK2, JAK3, and TYK2) become activated and phosphorylate signal transducer and activator of transcription (STAT) proteins, which subsequently translocate to the nucleus to regulate gene transcription involved in inflammation, immune cell activation, and barrier dysfunction. By inhibiting JAK activity, these agents block downstream signaling of multiple cytokines implicated in AD, including IL-4, IL-13, IL-22, IL-31, thymic stromal lymphopoietin (TSLP), and interferon-γ (IFN-γ) [13]. Importantly, several of these cytokines also directly interact with cutaneous sensory neurons expressing specific cytokine receptors, contributing to neuronal hypersensitivity and amplification of itch signaling. IL-31, a key pruritogenic cytokine, activates IL-31 receptor A on peripheral sensory neurons, while IL-4 and IL-13 enhance neuronal responsiveness to pruritogens through JAK1-dependent pathways. In addition, keratinocyte-derived TSLP can directly stimulate pruriceptive neurons and promote neurogenic inflammation. Through inhibition of JAK signaling, JAK inhibitors such as abrocitinib, baricitinib, and upadacitinib are therefore able to modulate not only inflammatory immune pathways but also neuroimmune interactions that drive itch perception and scratching behavior in AD. Through this broader immunomodulatory effect compared with single-cytokine blockade, JAK inhibitors can simultaneously reduce type-2 inflammation, pruritus signaling, and epidermal barrier impairment. Their oral administration, rapid onset of action, and broad immunomodulatory profile make them particularly attractive for addressing unmet needs in difficult-to-treat sites [14]. Early evidence from randomized clinical trials (RCTs) and real-world studies has demonstrated rapid improvement in skin clearance and symptom control, including itch, sleep disturbance, and quality of life, even in those regions historically considered less responsive [15].

In this narrative review, we provide an overview of current real-world evidence (RWE) on the use of JAK inhibitors for the treatment of AD in difficult-to-treat areas, focusing on efficacy, safety, and patient-reported outcomes across different anatomical regions.

2. Materials and Methods

This study was conducted as a structured narrative review aimed at summarizing and critically appraising RWE regarding the efficacy and safety of JAK inhibitors—specifically abrocitinib, baricitinib, and upadacitinib—in the management of AD involving difficult-to-treat anatomical areas. For the purposes of this review, difficult-to-treat areas were operationally defined as anatomical regions historically associated with therapeutic refractoriness, disproportionate symptom burden, functional impairment, or increased psychosocial impact. These included the head and neck, face, hands, feet, genital and intertriginous regions, as well as periocular and perioral areas. A comprehensive literature search was

conducted across PubMed, Ovid MEDLINE, Scopus, Embase, and the Cochrane Library, including articles published up to 31 December 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text terms. Queries included the names of the targeted JAK inhibitors ("abrocitinib," "baricitinib," "upadacitinib") in combination with terms such as "atopic dermatitis," "eczema," "real-world," "real-life," "difficult-to-treat," "refractory," "head and neck," "face," "hands," "feet," "genital," and "intertriginous." Boolean operators (AND/OR) were used to optimize search sensitivity and specificity. Titles and abstracts were screened for relevance, followed by full-text assessment of potentially eligible studies. To reduce selection bias, two independent authors (G.L. and M.N.) performed the screening of retrieved titles and abstracts, as well as a full-text eligibility assessment. Any discrepancies were resolved through discussion and consensus. A total of 412 records were initially identified through database searching. After removal of duplicates, 276 records remained for title and abstract screening. Of these, 224 were excluded for not meeting eligibility criteria. Fifty-two full-text articles were assessed for eligibility, and 30 were excluded following full-text review due to lack of regional stratification, absence of real-world data, exclusive focus on generalized disease without anatomical analysis, conference-only publications, non-English language, or duplicate cohort reporting. Ultimately, 22 studies met the predefined inclusion criteria and were included in the qualitative synthesis. Eligible studies consisted of real-world clinical investigations involving patients with AD treated with JAK inhibitors and reporting outcomes stratified by specific anatomical regions. Accepted study designs included prospective and retrospective observational cohorts, multicenter registries, and case series. Primary randomized controlled trial (RCT) efficacy analyses were excluded to maintain focus on routine clinical practice; however, post hoc regional analyses of RCTs were considered when they provided anatomically stratified data directly relevant to difficult-to-treat areas. Studies were excluded if they addressed exclusively generalized disease without site-specific analysis, were preclinical investigations, narrative reviews, editorials, or conference abstracts without full-text publication, or were not published in English. Reference lists of all eligible articles were manually screened to identify additional relevant studies not captured in the primary search. Given the narrative design of this review and the heterogeneity of study populations, regional outcome measures, and follow-up durations, no formal risk-of-bias assessment or quantitative meta-analysis was performed. The objective was to provide a structured qualitative synthesis of available real-world data rather than pooled effect estimates. This study is based exclusively on previously published literature and did not involve new data collection or human subject research.

3. Results

Results are summarized in Table 1.

Table 1. Overview of real-world evidence on JAK inhibitors (abrocitinib, baricitinib, and upadacitinib) for atopic dermatitis involving difficult-to-treat anatomical regions. Study design, population characteristics, anatomical sites involved, regional outcome measures, and principal site-specific findings are summarized.

Ref	Study (First Author, Year)	Drug	Design	Population	Difficult Area(s)	Regional Assessment	Key Regional Findings
ABROCITINIB							
[16]	Kamphuis et al., 2024 (BioDay Registry)	Abrocitinib	Registry	103 AD	Hands	HECSI	Progressive HECSI reduction to W28; high response rates

Table 1. *Cont.*

Ref	Study (First Author, Year)	Drug	Design	Population	Difficult Area(s)	Regional Assessment	Key Regional Findings
[17]	Gargiulo et al., 2024 (il-AD Study)	Abrocitinib	Multicenter cohort	85 AD	Face/neck, hands, genital	Regional EASI	77.7% EASI-75 at W16; deep responses observed
[18]	Olydam et al., 2023	Abrocitinib	Prospective real-world cohort	41 AD (73.2% prior targeted failure)	Regionally predominant AD	EASI, IGA, NRS-pruritus	Median EASI 14.3 → 4.0 at 28W($p < 0.0001$); EASI-50/75/90 41.5/31.7/29.6%; NRS 7.0 → 3.0; 41.5% discontinuation
[19]	Li et al., 2024	Abrocitinib	Prospective	12 CHE (3 atopic subtype)	Hands	HECSI	HECSI-90 in 100% at W16; marked pruritus reduction
[20]	Napolitano et al., 2025	Abrocitinib	Multicenter retrospective	12 AD difficult-to-treat areas	HN 75%, hands 75%, genital 58%; >2 areas 67%	Regional EASI; site persistence	Genital 58.3% → 8.3%; HN 75% → 8.3%; hands 75% → 25% at W16
[21]	Santosa et al., 2023	Abrocitinib	Case reports (n = 2)	2 AD	Dupilumab-associated HND	Clinical	Rapid craniofacial clearance within W4
BARICITINIB							
[22]	Boesjes et al., 2022 (Dutch BioDay)	Baricitinib	Registry	51 AD (74.5% prior dupilumab)	Severe treatment-experienced AD	EASI, NRS-pruritus	EASI 18.3 → 11.1 at W16; 29.4% EASI ≤ 7; 43.2% discontinuation
[23]	Carrascosa et al., 2024 (BREEZE-AD7)	Baricitinib 4 mg	Post hoc regional analysis (Phase III RCT)	Itch-dominant AD subgroup	HN, trunk, UL, LL	Regional EASI; EASI-75 by site	W16 EASI-75: HN 58.3%, trunk 69.2%, UL 61.5%, LL 87.5%
[24]	Hagino et al., 2023	Baricitinib 4 mg + TCS	Real-world cohort (Japan)	36 AD	HN, UL, LL, trunk	Regional EASI	W12 reduction: HN 56.9%, UL 68.3%, LL 80.7%, trunk 62.5%
[20]	Napolitano et al., 2024	Baricitinib	Comparative cohort	17 AD difficult-to-treat areas	HN 58.8%, hands 35.3%, genital 47.1%	Regional EASI; site persistence	EASI 23.88 → 4.75 at W16; no discontinuations
[25]	Lee et al., 2023	Baricitinib 4 mg (±reduction)	Case series	9 chronic hand/foot eczema	Hands/feet	IGA	9/9 achieved ≥2-grade IGA improvement; mean 3 weeks; AEs 33%
[26]	Lim et al., 2024	Baricitinib (add-on to dupilumab)	Retrospective cohort	12 AD add-on	HN dermatitis 66.7%	CR/PR; NRS	6 CR, 6 PR; 10/12 complete itch response
[27]	Rosenberg et al., 2022	Baricitinib 4 mg	Case report (2 pts)	2 severe chronic hand eczema	Hands	HECSI; QOLHEQ	HECSI 55 → 4 and 47 → 8 at W16; 1 discontinuation
UPADACITINIB							
[28]	Weidinger et al., 2025 (UP-TAINED)	Upadacitinib 15/30 mg	Prospective multicenter real-world	351 AD	Face (186), hands (142)	ADCT; EASI; vIGA-AD	W12 ADCT < 7 71%; M1 EASI-75 66.8%; vIGA 0/1 ~61%
[29]	Mortato et al., 2025	Upadacitinib 15/30 mg	Multicenter retrospective	150 AD	HN 82.6%	Global & regional EASI	W16 EASI-75 77.8%; HN EASI-75 68.5%; HN negative predictor
[30]	Kamphuis et al., 2023 (BioDay)	Upadacitinib 15/30 mg	Prospective multicenter cohort	38 AD (32 HE)	Hands	EASI; HECSI; ADCT	W16 EASI 17.2 → 4.8; HECSI 45.2 → 10.3; HECSI-75 59.3%
[31]	Melgosa Ramos et al., 2026	Upadacitinib 15/30 mg	Multicenter retrospective (>50 yrs)	38 AD	Special areas 63.2%	EASI; IGA; MDA	EASI 17.41 → 1.08 at W52; 84.6% maintained MDA
[32]	Bonzano et al., 2025	Upadacitinib 15 mg	Case report	1 acral AD	Hands + nail apparatus	HECSI	HECSI 102 → 7 at 1 month (~93% reduction)

Table 1. *Cont.*

Ref	Study (First Author, Year)	Drug	Design	Population	Difficult Area(s)	Regional Assessment	Key Regional Findings
[33]	Yang et al., 2023	Upadacitinib 15 mg	Case series	6 AD (dupilumab-refractory)	Face/neck	EASI; DLQI; ADCT	W12 EASI 8.1 → 0.73; 100% EASI-75; no AEs
[34]	Licata et al., 2022	Upadacitinib 15 mg BID	Case series	3 AD	Face/neck	Clinical	Rapid improvement 4–8 weeks post-dupilumab
[35]	Licata et al., 2023	Upadacitinib 15 mg	Case series	4 adolescents	Eyelids	EASI; DLQI	Complete eyelid resolution by W8
[36]	Hagino et al., 2024	Upadacitinib 30 mg	Dose-escalation real-world	23 AD	HN + other regions	Regional EASI	W4 EASI-75 68.2%; W12 66.7%; significant regional improvement

3.1. Abrocitinib

Abrocitinib, an oral selective JAK1 inhibitor, has emerged as an effective therapeutic option for moderate-to-severe AD, characterized by a rapid onset of action and broad cytokine modulation (IL-4, IL-13, IL-31, IFN-γ, TSLP). These pharmacodynamic features make it particularly well-suited for phenotypes driven by intense pruritus, mixed inflammatory pathways, and localized barrier disruption, which are frequently concentrated in difficult-to-treat anatomical regions such as the hands, face/neck, and genital areas. The BioDay Registry (n = 103) provides the largest real-world assessment of abrocitinib to date and includes a treatment-resistant population: 80.6% previously treated with dupilumab and 36.9% previously treated with upadacitinib [16]. At W28, 81.8%, 57.6%, and 18.2% of patients achieved a $\geq$50%, $\geq$75%, and $\geq$90% reduction from baseline in the Eczema Area and Severity Index (EASI) score (EASI-50, EASI-75, and EASI-90), respectively [16]. In a subgroup of patients with concomitant hand eczema (HE), disease severity assessed by the HECSI score showed a marked reduction from a mean score of 27.4 at baseline to 15.1 at W4 and further to 7.7 at W28. Response rates were high: at W4, HECSI-50, HECSI-75, and HECSI-90 were achieved by 65.2%, 52.2%, and 43.5% of patients, respectively; at W16, these increased to 86.7%, 66.7%, and 60.0%; and at W28, to 80.0%, 80.0%, and 70.0%, respectively [16]. Additional large-scale real-world data derive from the multicenter il-AD study by Gargiulo et al., in which 78.8% of participants (n = 85) exhibited involvement of at least one difficult area, most commonly the face/neck, hands, or genital region; 45.9% had hand involvement [17]. After W16 of abrocitinib treatment (100 mg or 200 mg daily), 77.7% achieved EASI-75, 49.4% reached EASI-90, and 24.7% attained EASI-100 [17]. An absolute EASI score of $\leq$7 and $\leq$3 was reached by 82.4% and 63.5% of patients, respectively, while 61.2% achieved an Investigator's Global Assessment (IGA) score of 0 or 1 [17]. Additional RWE comes from a prospective cohort of 41 adults with moderate-to-severe AD treated with abrocitinib in routine practice [18]. The population was highly treatment-experienced: 73.2% had failed prior targeted therapies, including dupilumab (31.7%), tralokinumab (7.3%), baricitinib (17.1%), and upadacitinib (17.1%), and 43.9% had received $\geq$4 prior systemic agents. After a median follow-up of 28 weeks, median EASI decreased from 14.3 at baseline to 4.0 at last review (median reduction −73.5%) [18]. At last evaluation, 41.5%, 31.7%, and 29.6% achieved EASI-50, EASI-75, and EASI-90, respectively, while 53.7% reached EASI $\leq$ 7. Median NRS-pruritus improved from 7.0 to 3.0, with 70.7% achieving NRS $\leq$ 4; 22.0% achieved IGA 0/1 [18]. Treatment was discontinued in 41.5% of patients after a median of 18 weeks, mainly due to ineffectiveness (41.2%) or adverse events (41.2%) [18]. Among difficult areas, the hands represent one of the most challenging sites to manage. A prospective observational study by Li et al. (2024) evaluated abrocitinib in 12 adults with chronic hand eczema (CHE) who had failed multiple systemic treatments, including cyclosporine, methotrexate, corticosteroids, and in several cases dupilumab [19].

Patients received abrocitinib 100 mg once daily for 16 weeks. By W4, half achieved HECSI-75; by W16, all reached HECSI-90. Median HECSI decreased from 136.0 at baseline to 3.0 at W16 [19]. WI-NRS improved from a median of 8.5 to 0, with all patients reporting scores ≤ 2 and eight reporting no itch. Nine patients achieved IGA 0/1 with at least a two-grade improvement [19]. Additional site-focused data derive from a retrospective multicenter Italian study including adults with moderate-to-severe AD and involvement of at least one sensitive area (head/neck, hands, genitalia, face) treated for $\geq$W16 [20]. Among 78 treated patients, 29 met inclusion criteria and 12 received abrocitinib. Baseline involvement included head/neck 75%, hands 75%, genitalia 58.33%, and face 16.67%, with 66.67% presenting > 2 sensitive areas [20]. Mean EASI decreased from 21.25 to 8.45 at W4 and 4.18 at W16. DLQI improved from 19.58 to 7.45 and 4.64; P-NRS from 7.83 to 2.82 and 1.64 at W4 and W16, respectively [20]. Persistence of difficult-to-treat involvement declined markedly across all regions, and regional EASI subscores improved in head/neck (2.29 $\rightarrow$ 0.74 $\rightarrow$ 0.38), upper limbs (3.68 $\rightarrow$ 1.52 $\rightarrow$ 0.64), trunk (5.53 $\rightarrow$ 1.93 $\rightarrow$ 0.93), and lower limbs (6.17 $\rightarrow$ 1.77 $\rightarrow$ 0.69) [20]. In dupilumab-associated head and neck dermatitis (HND), two case reports described the effectiveness of abrocitinib [21]. In the first case, a 51-year-old woman developed progressive facial erythema eight weeks after starting dupilumab, with persistence for one year despite TCS, TCI, antifungals, and a trial of baricitinib. Switching to abrocitinib 200 mg daily led to a marked improvement within W4, maintained for six months [21]. In the second case, a 41-year-old man developed HND within three months of dupilumab initiation. After limited response to antifungals and transient improvement on baricitinib, abrocitinib induced substantial clearance within W4. Dose tapering to 200 mg every other day due to mild transaminase elevation did not compromise disease control over six months [21].

3.2. Baricitinib

Baricitinib, a JAK1/JAK2 inhibitor, is approved for the treatment of moderate-to-severe AD and modulates multiple cytokines involved in type-2-skewed inflammation, including IL-4, IL-13, IL-22, IL-31, and TSLP. These properties have prompted investigation into its role in regionally complex and difficult-to-treat AD phenotypes. Early prospective evidence from the Dutch BioDay registry evaluated 51 adults with moderate-to-severe AD treated with baricitinib in routine clinical practice [22]. The cohort was highly treatment-experienced, with 38/51 (74.5%) previously discontinuing dupilumab due to inefficacy (42.1%), adverse events (31.6%), or both (26.3%). After 16 weeks, mean EASI significantly decreased from 18.3 to 11.1 ($p < 0.0001$), and mean NRS-pruritus from 6.6 to 5.3 ($p < 0.0001$). The probability of achieving EASI ≤ 7 at week 16 was 29.4%, while 20.5% achieved NRS-pruritus ≤ 4. Treatment discontinuation occurred in 22/51 patients (43.2%), due to ineffectiveness (33.3%), adverse events (9.8%), or both (2.0%). No significant differences in effectiveness were observed between dupilumab non-responders and dupilumab responders or naïve patients [22]. Further insights into regional responsiveness derive from a body region-specific analyses of the BREEZE-AD7 phase III trial focusing on the "BARI itch-dominant" subgroup (baseline body surface area $\leq$ 40% and Itch NRS ≥ 7) [23]. In this subgroup, mean overall BSA was 30.4%, while mean regional BSA ranged from 23.5% (lower extremities) to 40.3% (head/neck). Mean baseline EASI region scores were highest in the trunk (24.0), upper extremities (23.5), and head/neck (23.3), and lower in the lower extremities (15.7) [23]. At W16, baricitinib 4 mg demonstrated consistent regional efficacy. EASI-75 was achieved in 58.3% of patients in the head/neck region (vs. 37.5% placebo), 69.2% in the trunk (vs. 40.6%), 61.5% in the upper extremities (vs. 18.8%), and 87.5% in the lower extremities (vs. 40.6%) [23]. Correspondingly, least-squares mean percent change from baseline in regional EASI scores at week 16 was -65.0% (head/neck),

−69.1% (trunk), −59.9% (upper extremities), and −81.9% (lower extremities), all exceeding placebo responses [23]. Complementary RWE derives from a Japanese cohort including 36 adolescents and adults treated with baricitinib 4 mg/day plus topical corticosteroids [24]. Median percent reduction in total EASI was 69.19% at W4 and 69.98% at W12. Site-specific analyses showed differential regional responsiveness: at W12, median EASI reduction was 56.9% for the head and neck, 68.3% for the upper limbs, 80.7% for the lower limbs, and 62.5% for the trunk. EASI-75 at W12 was achieved in 27.8% (head/neck), 41.7% (upper limbs), 66.7% (lower limbs), and 30.6% (trunk) [24]. Baseline head and neck EASI was negatively correlated with percent reduction at W4, while baseline lower limb EASI was positively correlated with percent reduction at W12 [24]. Additionally, site-focused data derive from a multicenter retrospective cohort including 17 patients treated with baricitinib for ≥16 weeks and presenting involvement of at least one difficult-to-treat area (head/neck, hands, genitalia, or face) [20]. At baseline, head and neck involvement was observed in 58.82%, hands in 35.29%, genitalia in 47.06%, and >2 sensitive areas in 52.94% [20]. Mean EASI decreased from 23.88 to 8.63 at W4 and 4.75 at W16. Mean DLQI improved from 20.13 to 4.06 at W16, and mean P-NRS from 8.63 to 2.19. Persistence of difficult-to-treat involvement declined markedly across regions, with head and neck involvement decreasing to 11.76% and hand involvement to 0% by W16. No treatment discontinuations were reported [20]. Further RWE in acral disease derives from a retrospective case series of nine adults with chronic hand and/or foot eczema (CHFE) refractory to conventional systemic therapy [25]. The cohort included isolated hand, isolated foot, and combined involvement, with vesicular, atopic, and hyperkeratotic subtypes. Baricitinib 4 mg daily was initiated, with dose reduction to 2 mg in four patients. All nine patients achieved the primary endpoint (IGA 0–1 or ≥2-grade improvement) within a mean of 3 weeks (range 2–8). Adverse events were reported in 3/9 patients (33%), including leukopenia, dyslipidemia, and acne; no serious adverse events occurred [25]. Additional case-based evidence derives from a Korean retrospective cohort including 34 adults with moderate-to-severe AD, of whom 12 received baricitinib as add-on therapy to ongoing dupilumab due to unsatisfactory response [26]. In the add-on group, complete response (>95% improvement) was observed in six patients and partial response (>50% improvement) in six patients [26]. Eight patients (66.7%) had head and neck dermatitis; among them, 2 achieved complete response, 5 partial response, and 1 showed no response in that specific region [26]. Pruritus improved rapidly, with 10 patients achieving complete itch improvement (NRS 0–1) and two partial improvement; mean time to complete itch response was 2.6 weeks [26]. Further case-based data derive from two patients with severe chronic hand eczema treated with baricitinib 4 mg daily [27]. In the first case (baseline HECSI 55), HECSI decreased to 4 at 16 weeks, with QOLHEQ improving from “strongly impaired” to “not at all impaired.” In the second case (baseline HECSI 47), HECSI decreased to 8 at 16 weeks, with QOLHEQ improving from “moderately impaired” to “not at all impaired.” Baricitinib was tapered and subsequently discontinued in the second case due to a bacterial corneal ulcer [27].

3.3. Upadacitinib

Upadacitinib, a selective JAK1 inhibitor, has emerged as one of the most effective targeted therapies for moderate-to-severe AD, demonstrating rapid onset, durable control, and broad anti-inflammatory activity. A particularly important aspect is its performance in difficult-to-treat anatomical regions, such as the face, neck, hands, feet, and genital/intertriginous areas, which frequently show suboptimal response to biologics or conventional systemic therapies. These pharmacological properties translate into consistent clinical benefits across real-world settings, where upadacitinib has demonstrated early, robust, and anatomically versatile improvement, including in the most refractory sites. The

German prospective, multicenter UP-TAINED study evaluated 351 adolescents and adults with moderate-to-severe AD treated with upadacitinib 15 or 30 mg once daily in routine clinical practice [28]. At W12, 71.0% of patients achieved disease control, defined as an Atopic Dermatitis Control Tool (ADCT) score < 7, a proportion sustained at 12 months (70.9%). High levels of skin clearance were observed early. An EASI score ≤ 3 was achieved by 60.6% of patients after 4 weeks and 68.1% after 12 months [28]. At month 1, 66.8%, 47.0%, and 22.6% of patients achieved EASI-75, EASI-90, and EASI-100, respectively; these rates increased at month 3 to 77.2%, 60.5%, and 30.8%, and were maintained at month 12 (76.5%, 58.8%, and 34.5%) [28]. Among patients with moderate-to-severe facial (n = 186) or hand eczema (n = 142) at baseline, 60.8% (101/166) and 63.8% (83/101), respectively, achieved clear or almost clear skin, defined as validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD) 0/1 in the affected region after 4 weeks. At 12 months, response rates increased to 75.8% (face) and 76.7% (hands) [28]. Further confirmation of upadacitinib effectiveness in patients with high disease burden and frequent involvement of difficult-to-treat areas derives from the large multicenter Italian retrospective cohort reported by Mortato et al. [29]. This real-world study included 150 adults with moderate-to-severe AD treated across eight referral centers, of whom 82.6% (124/150) presented head and neck involvement at baseline. Patients received upadacitinib monotherapy at either 15 mg (65.4%) or 30 mg daily (34.6%). The mean baseline EASI score was 18.6 $\pm$ 10.1 and significantly decreased to 2.8 $\pm$ 4.7 at W16, with sustained improvement through W52 and W104 [29]. At W16, 77.8%, 57.8%, and 39.2% of patients achieved at least a 75%, 90%, and 100% reduction in EASI from baseline (EASI-75, EASI-90, and EASI-100), respectively. These responses were maintained over time, with EASI-75 achieved in 77.7% and EASI-100 in 51.3% of patients at W52 [29]. When focusing specifically on head and neck involvement, regional responses were slightly lower compared with overall outcomes but remained clinically meaningful. At W16, head and neck EASI-75, EASI-90, and EASI-100 were achieved by 68.5%, 56.2%, and 52.6% of patients, respectively; these rates increased to 74.6%, 67.0%, and 62.0% at week 32 and remained stable in long-term follow-up [29]. Univariate logistic regression analyses identified higher baseline EASI as a positive predictor of achieving EASI-75 at W16 and W32 (OR 1.06, 95% CI 1.01–1.13, p = 0.032). Conversely, head and neck involvement emerged as a negative predictor for EASI-75 and EASI-90 responses at later time points, while prior systemic therapy—particularly cyclosporine—was associated with a reduced likelihood of achieving complete clearance (EASI-100) [29]. Despite this relative regional refractoriness, the majority of patients with head and neck dermatitis achieved substantial and sustained improvement, confirming that upadacitinib maintains robust effectiveness even when craniofacial involvement represents the dominant disease site [29]. Complementary RWE derives from the Dutch BioDay registry, a prospective multicenter observational cohort evaluating upadacitinib in daily clinical practice, with a specific focus on concomitant hand eczema (HE) in patients with AD [30]. The study included 38 adults with moderate-to-severe AD, of whom 32 (84.2%) presented with concomitant HE. The population was highly treatment-experienced: 92.1% had previously received ≥ 2 systemic immunosuppressants and 86.8% had prior exposure to dupilumab. Baseline mean EASI was 17.2 (SD 12.3), while mean HECSI in the HE subgroup was 45.2 (SD 50.4) [30]. At W16, significant improvements were observed across both global AD and hand-specific outcomes. Mean EASI decreased to 4.8 (SD 4.5), with EASI-75 achieved by 50.0% and EASI-90 by 25.0% of patients [30]. Absolute disease control (EASI ≤ 7) was reached by 75.0%. Pruritus improvement was also clinically meaningful, with 62.5% achieving P-NRS ≤ 4 and 68.8% reaching ADCT < 7. In patients with concomitant HE, mean HECSI decreased from 45.2 to 10.3 at W16 [30]. HECSI-50, HECSI-75 and HECSI-90 were achieved by 74.1%, 59.3%, and 37.0% of patients, respectively. Moreover, 74.1% were rated as "almost clear" on

the Photographic Guide. Quality of life related to hand eczema, assessed using QOLHEQ, improved significantly, with 57.9% achieving the minimally important change at W16 [30]. Importantly, sub-analyses showed no significant differences in response between patients with and without concomitant irritant contact dermatitis, suggesting that upadacitinib may be effective across different etiological subtypes of HE within AD [30]. Additional data derive from a multicenter retrospective study conducted in six Spanish hospitals including 38 adults aged > 50 years (mean age 63.9 ± 10.2) with moderate-to-severe AD treated with upadacitinib 15 or 30 mg daily [31]. Special area involvement was present in 63.2% of patients, including face/neck (44.7%), hands (36.8%), and genital region (13.2%) [31]. Mean baseline EASI was 17.41 and decreased to 4.22 at W4, 3.00 at W16, and 1.08 at W52. IGA improved from 3.00 at baseline to 1.00 at W4 and 0.00 at W52. P-NRS declined from 7 at baseline to 2 at W4 and 0 at W52, while DLQI improved from 16.11 to 3.27 at W4 and 0.57 at W52. Body surface area (BSA) decreased from 22.92% at baseline to 5.05% at W4 and 1.09% at W52 [31]. By W16, 25/38 patients (65.8%) achieved minimal disease activity (MDA). Among the 13 patients who had reached MDA and had available data at W52, 11 (84.6%) maintained MDA (p = 0.011) [31]. No severe infections, neoplasms, herpes zoster, or major adverse cardiovascular events were reported. One patient discontinued treatment due to headache. Mild-to-moderate acne occurred in six patients, and three developed transient lymphopenia without treatment discontinuation [31]. Beyond cutaneous involvement of the hands, difficult-to-treat acral AD may include periungual and nail-associated changes. Bonzano et al. reported a case of a 29-year-old woman with long-standing AD with prevalent involvement of the face and hands, presenting with severe atopic HE and associated nail dystrophy/periungual changes [32]. Patch testing was negative and prior therapies included potent/ultrapotent TCS, TCI, conventional immunosuppressants, and phototherapy [32]. The patient was referred for an abrupt exacerbation of AD (EASI > 24) and showed severe HE despite ongoing clobetasol ointment, with a baseline HECSI of 102 [32]. Upadacitinib 15 mg once daily was initiated. After 1 month, HE markedly improved, with a 93% reduction in HECSI (from 102 to 7). Clinical response was maintained at 3 months, with nearly complete resolution of nail dystrophy and periungual changes [32]. A case series by Yang et al. described six adolescents and young adults (mean age 18.7 ± 7.7 years) with persistent facial and neck AD after 14–20 weeks of dupilumab therapy who were switched to upadacitinib 15 mg once daily for 12 weeks [33]. At baseline (prior to upadacitinib), mean EASI was 8.1 ± 0.66, with facial and cervical erythema and pruritus representing the dominant residual disease [33]. After 12 weeks of upadacitinib treatment, mean EASI decreased to 0.73 ± 0.56, with all patients achieving EASI-75 and three (50%) achieving EASI-90. Mean DLQI improved from 12.5 ± 6.24 to 0.67 ± 0.75, ADCT from 11.5 ± 3.15 to 0.33 ± 0.75, and P-NRS from 6.83 ± 0.37 to 0 [33]. No AEs were reported during the 12-week treatment period. Peripheral blood eosinophil counts decreased from 2.65 ± 3.24 to 1.42 ± 2.42 × 10^9/L [33]. Additional case-based evidence derives from a case series by Licata et al., describing three adults with persistent facial AD during dupilumab therapy who were subsequently treated with upadacitinib [34]. The first case involved a 26-year-old man who developed sudden facial relapse after 40 weeks of dupilumab despite previous clinical improvement. Systemic and topical corticosteroids failed to control the relapse. Switching to upadacitinib 15 mg twice daily resulted in marked improvement within 4 weeks [34]. The second case concerned a 38-year-old woman who developed persistent facial and neck dermatitis during dupilumab treatment, suspected to represent dupilumab-associated regional dermatosis. One month of itraconazole was ineffective. After discontinuation of dupilumab and initiation of upadacitinib 15 mg twice daily, notable clinical improvement was observed at 2 months [34]. The third case described a 23-year-old woman who discontinued dupilumab after 28 weeks due to recurrent bilateral

conjunctivitis and concomitant facial eczema relapse. Upadacitinib 15 mg twice daily led to resolution of facial lesions within 4 weeks. No adverse events were reported in this series [34]. Periocular involvement has been further described in a case series by Licata et al., including four adolescents (ages 12–17 years) with moderate-to-severe AD and persistent primary atopic blepharitis during dupilumab therapy [35]. At baseline, mean EASI was 20, mean DLQI was 25, and mean P-NRS was 8. After 36 weeks of dupilumab, partial improvement of generalized eczema was observed; however, eyelid dermatitis persisted, with EASI values ranging from 9 to 15 at the time of switch [35]. Following discontinuation of dupilumab, patients were started on upadacitinib 15 mg once daily. After 4 weeks, marked clinical improvement and resolution of pruritus were observed. After 8 weeks of upadacitinib treatment, EASI decreased to values ranging between 2 and 6, with complete clinical resolution of eyelid eczema. Treatment was maintained for approximately 20 weeks without significant AEs [35]. Dose escalation of upadacitinib has also been investigated in real-world practice. In a Japanese cohort of 23 patients with moderate-to-severe AD showing insufficient response to upadacitinib 15 mg, the dose was increased to 30 mg once daily [36]. At the time of dose escalation (W0), median total EASI was 12.4 [9.95–19.5], and median head and neck EASI was 2.4 [1.55–3.4]. Following escalation to 30 mg, significant reductions were observed in total and site-specific EASI scores [36]. Median head and neck EASI decreased to approximately 1.1 at W4 and 1.2 at W12. Achievement rates of EASI-75 increased from 4.3% at W0 to 68.2% at W4 and 66.7% at W12, while EASI-90 increased from 0% to 18.2% and 38.1% at W4 and W12, respectively [36]. Although percent reduction in head and neck EASI was lower compared with the trunk at W4, dose escalation resulted in significant clinical improvement across all anatomical regions [36].

4. Discussion

The growing body of RWE summarized in this review highlights the expanding role of JAK inhibitors in managing difficult-to-treat anatomical areas of AD, a setting in which therapeutic outcomes have historically been suboptimal compared with trunk and limb involvement. Across heterogeneous real-life populations—often characterized by prior biologic exposure, regional refractoriness, and comorbidities—abrocitinib, baricitinib, and upadacitinib consistently demonstrated clinically meaningful improvement in areas marked by structural, environmental, and immunologic complexity. Collectively, these findings support a shift toward a phenotype-driven and region-oriented approach to systemic therapy selection in AD [37]. These real-world findings appear broadly consistent with the efficacy reported in pivotal clinical trials of JAK inhibitors for AD. In randomized controlled trials, abrocitinib, baricitinib, and upadacitinib have demonstrated rapid improvements in EASI and pruritus scores, with substantial proportions of patients achieving high levels of disease control within the first 16–24 weeks of treatment. However, the interpretation of these findings requires caution. Most available real-world studies are observational, frequently include relatively small cohorts, and often involve heterogeneous populations with different degrees of prior systemic or biologic exposure. In addition, the definition of "difficult-to-treat areas" and the methods used to assess regional outcomes vary considerably across studies. These factors introduce substantial methodological heterogeneity and limit the possibility of drawing direct comparisons between different JAK inhibitors.

A recurring concept emerging from real-life studies is that difficult-to-treat areas do not merely represent "more severe" AD, but rather distinct inflammatory ecosystems. The head and neck, for instance, may display mixed immune activation (including Th2, Th1 and Th22-related pathways), local barrier vulnerability, and microbial factors, which likely contribute to paradoxical erythema and/or incomplete responses observed with IL-4Rα blockade in some patients. Similarly, acral sites, particularly the hands, are subject to

repeated mechanical trauma, irritant exposure, and persistent barrier disruption, fostering chronicity and therapeutic resistance. In this setting, JAK inhibitors are uniquely positioned because they modulate multiple cytokine pathways implicated in AD pathogenesis and pruritus, offering broader immunologic coverage than biologics that primarily target type-2 inflammation. Although these hypotheses remain partially inferential, emerging translational data, they support the concept that regional immune heterogeneity may influence therapeutic responsiveness [37–39]. An additional aspect potentially relevant to disease chronicity and relapse concerns the role of tissue-resident memory T cells (TRM). These long-lived lymphocytes persist within previously affected skin and are thought to contribute to the rapid reactivation of inflammation after treatment discontinuation or environmental triggers. Although direct evidence evaluating the effect of JAK inhibitors on TRM populations in atopic dermatitis is currently limited, the broad cytokine inhibition exerted by these agents may indirectly influence TRM activity. In particular, cytokines such as IL-4, IL-13, IL-22, and interferon-γ, which are involved in TRM activation and maintenance, signal through JAK-dependent pathways. By interfering with these signaling cascades, JAK inhibitors may reduce the inflammatory signals that sustain pathogenic memory responses in the skin. Future translational studies investigating the interaction between JAK inhibition and TRM dynamics may therefore provide important insights into the long-term control of disease recurrence in atopic dermatitis.

Among the agents discussed, upadacitinib is supported by the largest and most consistent real-world datasets currently available, demonstrating high and sustained response rates across multiple anatomical regions, including the face/neck and hands, even in heavily pretreated cohorts. Nevertheless, the apparent differences in response magnitude between JAK inhibitors observed across studies should not be interpreted as definitive evidence of superior effectiveness. Variability in cohort size, baseline disease severity, regional disease distribution, prior biologic exposure, and dosing strategies may strongly influence reported outcomes. Consequently, the current literature does not allow the establishment of a clear hierarchy of efficacy among different JAK inhibitors in difficult-to-treat anatomical areas. Importantly, real-life observations also suggest that treatment individualization, particularly dose escalation in patients with suboptimal initial response, may optimize outcomes in regionally complex disease, supporting a flexible strategy tailored to inflammatory burden and anatomical distribution [28–36]. However, cross-study comparisons should be interpreted with caution, as differences in cohort size, baseline severity, prior biologic exposure, dosing strategies, and regional outcome assessment limit the ability to establish a definitive hierarchy of effectiveness among JAK inhibitors. Abrocitinib likewise demonstrated compelling effectiveness in difficult-to-treat AD, with particularly consistent signals in hand eczema and multiregional involvement. Across both small prospective experiences and larger registries, abrocitinib provided rapid and marked improvement in pruritus and objective severity measures, including in biologic-experienced and biologic-refractory patients. Notably, reports of efficacy in dupilumab-associated head and neck dermatitis further reinforce the concept that selective JAK1 inhibition can be highly effective in craniofacial phenotypes characterized by intense itch and mixed inflammatory signatures, where IL-4/IL-13 blockade may be insufficient [16–21]. Moreover, the consistency of hand-specific outcomes across registries and prospective cohorts reinforces the potential role of abrocitinib in acral-dominant phenotypes, particularly when intense pruritus and functional impairment are central drivers of disease burden [16–21]. Baricitinib demonstrated meaningful regional improvement in both clinical trial post hoc analyses and real-world cohorts, although response magnitude appeared more heterogeneous across anatomical sites in some datasets. Nevertheless, baricitinib still provided meaningful benefit in biologic-refractory and itch-dominant phenotypes, and regional analyses indi-

cated that clinically relevant improvement may be achieved even when baseline head and neck burden is disproportionately high. Taken together, these findings suggest that baricitinib remains a valuable option for selected patients, particularly where mixed-pathway activation and prominent pruritus dominate, although its regional response dynamics may require careful patient selection and expectation management [22–27]. Overall, the RWE reviewed here delivers practical clinical lessons. First, JAK inhibitors should be strongly considered when AD is region-dominant, particularly when the face/neck or hands are disproportionately affected, when biologics fail to achieve adequate regional control, or when pruritus remains severe and functionally limiting despite improvements in generalized eczema. Second, in anatomically sensitive regions, rapid itch suppression may be particularly relevant, as interruption of the itch–scratch cycle likely contributes not only to symptom relief but also to restoration of local barrier function and reduction in secondary inflammation. Third, the need for therapeutic flexibility, including switching within class and dose modulation in selected contexts, appears particularly relevant for anatomically complex or refractory phenotypes encountered in tertiary care. Safety findings across real-world cohorts were broadly consistent with data from pivotal clinical trials. Most adverse events were mild-to-moderate and included acneiform eruptions, transient laboratory abnormalities (such as lymphopenia or lipid changes), and occasional treatment discontinuations due to inefficacy or tolerability concerns [16–36]. Importantly, no unexpected safety signals specific to difficult-to-treat anatomical sites emerged from the available data. Nevertheless, longer-term pharmacovigilance in older patients and individuals with significant comorbidities remains essential.

In addition, particular attention should be paid to the risk of herpes zoster reactivation associated with JAK inhibitor therapy [40]. Increasing evidence from clinical trials and real-world studies indicates a higher incidence of herpes zoster in patients treated with JAK inhibitors compared with conventional systemic therapies or biologics. For this reason, recent recommendations from the Italian Society of Dermatology and Sexually Transmitted Infections (SIDeMaST) emphasize the importance of assessing varicella–zoster virus immunity and considering vaccination with the recombinant zoster vaccine prior to initiating JAK inhibitor therapy, particularly in patients aged $\geq$ 50 years or in those with additional risk factors. Incorporating preventive vaccination strategies into routine clinical practice may therefore further improve the safety profile of JAK inhibitors in patients with moderate-to-severe AD [40].

Several limitations must be acknowledged. The heterogeneity of real-world study designs, sample sizes, endpoints, and follow-up duration complicates direct comparisons across agents and limits the ability to define a hierarchy of effectiveness with certainty. Additionally, the lack of standardized regional outcome measures and uniform definitions of "difficult-to-treat" areas across studies represents a significant methodological limitation. Many cohorts lack standardized regional scoring systems, and mechanistic explanations for region-specific refractoriness remain incompletely understood. Long-term safety data in complex subgroups, especially older adults and patients with multiple comorbidities, remain limited in real-life reports. Moreover, optimal sequencing strategies between biologics and JAK inhibitors, and the role of combination or add-on approaches, have not been fully defined despite emerging clinical experiences. Another limitation of the available real-world evidence concerns the outcome measures used to assess treatment response. Most studies relied on global disease scores such as EASI, IGA, or pruritus numeric rating scales, which may not fully capture treatment effects in localized anatomical areas. As a result, improvements in difficult-to-treat sites may be under- or overestimated when evaluated using global metrics. In addition, some studies reported outcomes related to hand eczema within cohorts of patients with atopic dermatitis. Because chronic hand eczema

represents a heterogeneous clinical entity that may not always be directly attributable to AD, the interpretation of these findings should be made with caution. Nevertheless, these data were included in order to provide a comprehensive overview of difficult-to-treat anatomical involvement reported in the real-world literature. Future research should prioritize standardized assessment of difficult-to-treat regions (including harmonized regional EASI metrics and patient-reported outcomes), longer follow-up with structured safety reporting, and prospective real-world comparative studies that account for baseline localization patterns and prior biologic exposure. In parallel, integrating clinical regional phenotyping with mechanistic biomarkers may refine treatment selection and better explain why some anatomical sites respond differently to specific targeted interventions. From a clinical perspective, the available real-world evidence suggests that treatment decisions in AD should increasingly consider not only overall disease severity but also anatomical distribution of lesions. Region-dominant disease, particularly involving the face/neck or hands, may represent a distinct therapeutic scenario in which rapid itch suppression and broader cytokine modulation become particularly relevant therapeutic targets. In summary, RWE indicates that JAK inhibitors represent a significant advance in the management of AD involving difficult-to-treat areas. By providing rapid, multidimensional improvement, particularly in pruritus, and by demonstrating clinically meaningful effectiveness in anatomically challenging regions such as the face/neck, hands, and genital sites, these agents address key unmet needs that have long constrained therapeutic success. As RWE continues to accumulate and regional phenotyping becomes increasingly standardized, JAK inhibitors are emerging as central components of personalized treatment strategies for anatomically complex and refractory AD.

5. Conclusions

Difficult-to-treat anatomical areas represent a major unmet need in the management of AD, as they are frequently associated with persistent inflammation, disproportionate symptom burden, and reduced therapeutic responsiveness. The real-world evidence synthesized in this review consistently indicates that JAK inhibitors, abrocitinib, baricitinib, and upadacitinib, provide meaningful clinical benefits across anatomically complex regions, including the head and neck, hands, genital, and intertriginous areas. Beyond improvements in objective disease severity, rapid and sustained pruritus reduction emerged as a key therapeutic advantage, likely contributing to restoration of barrier integrity and interruption of the itch–scratch cycle, which is particularly relevant in sensitive sites. Although differences in study design and regional outcome assessment prevent definitive comparisons among agents, available data support the use of JAK inhibitors as valuable options in patients with region-dominant or biologic-refractory disease. Their broad cytokine modulation may be particularly advantageous in anatomical regions characterized by heterogeneous inflammatory pathways and environmental triggers. Importantly, safety findings from real-world cohorts remained consistent with clinical trial experience, with no site-specific safety concerns identified.

Future research should focus on standardized regional outcome measures, prospective comparative real-world studies, and biomarker-driven patient stratification to better define optimal treatment sequencing. Overall, JAK inhibitors are emerging as central components of a personalized, region-oriented therapeutic strategy for anatomically complex AD.

Author Contributions: Conceptualization, D.C., G.L., L.P., C.P. and M.N.; methodology, D.C., G.L., L.P., C.P. and M.N.; validation, C.P. and M.N.; formal analysis, D.C. and G.L.; investigation, D.C., G.L. and L.P.; data curation, D.C., G.L., L.P., C.P. and M.N.; writing—original draft preparation, D.C., G.L., L.P., C.P. and M.N.; writing—review and editing, D.C., G.L., L.P., C.P. and M.N.; visualization,

D.C., G.L., L.P., C.P. and M.N.; supervision, C.P. and M.N. All authors have read and agreed to the published version of the manuscript.

Funding: No funding was received to conduct this study.

Institutional Review Board Statement: Ethical review and approval were waived for this study because it is a narrative review based exclusively on previously published studies. No new human or animal data were collected, and no identifiable patient information was used.

Data Availability Statement: Data are reported in the current study.

Conflicts of Interest: Maddalena Napolitano acted as speaker, consultant and advisory board member for Sanofi, AbbVie, LEO Pharma, Amgen, Pierre Fabre, and Eli Lilly. Cataldo Patruno acted as investigator, speaker, consultant and advisory board member for AbbVie, Almirall, Amgen, Eli Lilly, Galderma, Incyte, La Roche-Posay, Leo Pharma, Novartis, Pfizer, Pierre Fabre, and Sanofi. No potential conflicts of interest were reported by the other authors.

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