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ADVERSE EFFECTS OF RITLECITINIB IN ADULTS AND ADOLESCENTS WITH ALOPECIA AREATA: A LITERATURE REVIEW

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ABSTRACT

Alopecia areata is a chronic, autoimmune disease characterized by non-scarring hair loss on the scalp, face, or body and affects approximately 2% of the global population. The condition often results in significant psychological distress, particularly among adolescents. Ritlecitinib, a first-in-class, oral, selective dual inhibitor of Janus kinase 3 (JAK3) and tyrosine kinase expressed in hepatocellular carcinoma (TEC) family kinases, was recently approved for the treatment of severe AA in adults and adolescents aged 12 years and older.

Background. Alopecia areata is characterized by non-scarring loss of scalp, face, or body hair. We investigated the efficacy and safety of ritlecitinib, an oral, selective dual JAK3/TEC family kinase inhibitor, in patients with alopecia areata.

Material and methods. A comprehensive search of databases, including PubMed and Google Scholar, was conducted using the keywords mentioned below.

Conclusions. The most commonly reported adverse effects of ritlecitinib in adults and adolescents with alopecia areata are headache, acne, and nasopharyngitis. These events are generally mild to moderate in severity and occur more frequently than with placebo. Other adverse effects observed include upper respiratory tract infections, urticaria, urinary tract infection, folliculitis, dizziness, and pyrexia. Laboratory abnormalities such as transient decreases in hemoglobin, neutrophil counts, platelets, and lymphocyte counts have been noted, but these changes tend to stabilize with continued treatment and are not typically associated with clinical sequelae.

Serious adverse events - including malignancy, major adverse cardiovascular events, serious infections are rare, with no increased incidence compared to placebo in clinical trials up to 24 months. No deaths, opportunistic infections, or pulmonary embolisms have been reported in adult or adolescent populations during these studies. Discontinuation due to adverse events is infrequent, and the overall safety profile is considered acceptable for long-term use in patients aged 12 years and older. Real-world pharmacovigilance data corroborate these findings, showing that headache, increased blood creatine phosphokinase, urticaria, acne, and upper respiratory infections are the most frequently reported adverse events.

KEYWORDS

Ritlecitinib, Alopecia Areata, JAK Inhibitors, Adverse Effects

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Introduction

Alopecia areata (AA) is a chronic, autoimmune, non-scarring hair loss disease that affects both children and adults, with a global prevalence of approximately 2%. The condition is characterized by the loss of immune privilege at the hair follicle, resulting in autoreactive $CD8^+$ T-cell–mediated damage to the follicular epithelium and subsequent hair loss. Clinical manifestations range from small, well-circumscribed patches of hair loss to complete loss of scalp (alopecia totalis) or body hair (alopecia universalis). The disease course is unpredictable, with many patients experiencing relapsing and remitting episodes of hair loss, and it often imposes substantial psychological and social burdens, especially among adolescents.

Despite its significant psychosocial impact, therapeutic options for AA have historically been limited. Conventional treatments, including corticosteroids, immunosuppressants, and contact immunotherapy, are often off-label, variably effective, and associated with safety or tolerability concerns. In recent years, the discovery of Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling dysregulation in AA pathogenesis has led to the development of targeted therapies. Ritlecitinib, a selective covalent inhibitor of JAK3 and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family of kinases, represents one of the most promising agents in this therapeutic class. On June, 23, 2023 ritlecitinib was approved by the U.S. Food and Drug Administration (FDA) for the treatment of severe alopecia areata in adults and adolescents 12 years.

Clinical evidence from the ALLEGRO program, including the pivotal phase 2b/3 and long-term phase 3 (ALLEGRO-LT) studies, has demonstrated that ritlecitinib is efficacious and generally well tolerated in adults and adolescents aged ≥12 years with moderate-to-severe AA. Importantly, ritlecitinib is currently the only approved systemic therapy for adolescents with severe AA, addressing a major unmet need in pediatric dermatology. However, as with all immunomodulatory treatments, concerns regarding potential adverse effects, including infections, malignancy, and cardiovascular events, necessitate careful long-term evaluation of its safety profile, particularly in younger populations.

Ritlecitinib is an oral, small-molecule immunomodulator that exerts its therapeutic effects in alopecia areata (AA) through selective, covalent inhibition of Janus kinase 3 (JAK3) and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family of kinases. The pathogenesis of AA involves the collapse of immune privilege at the hair follicle, followed by an autoimmune attack mediated by $CD8^+$ $NKG2D^+$ T cells and natural killer (NK) cells. These immune cells are activated by cytokines such as interleukin (IL)-15 and interferon-γ (IFN-γ), which sustain a self-amplifying inflammatory loop via the JAK-STAT signalling pathway. Inhibition of this pathway has therefore emerged as a promising therapeutic strategy to restore immune tolerance around the hair follicle.

Ritlecitinib acts by irreversibly binding to a unique cysteine residue (Cys-909) in the ATP-binding pocket of JAK3, a residue that is not conserved in other JAK isoforms (JAK1, JAK2, TYK2) - conferring high target selectivity. Through this mechanism, ritlecitinib selectively blocks intracellular signalling of the common γ-chain cytokine receptor family, which includes receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. These cytokines are critical for the development, activation, and survival of cytotoxic and memory T cells, as well as NK cells. By attenuating their downstream STAT phosphorylation and transcriptional activity, ritlecitinib effectively reduces the activation and proliferation of autoreactive lymphocytes that drive follicular inflammation.

In addition to JAK3 inhibition, ritlecitinib also targets the TEC kinase family, which includes interleukin-2-inducible T-cell kinase (ITK), TEC, Bruton's tyrosine kinase (BTK), TXK, and BMX. These kinases mediate intracellular signalling downstream of the T-cell receptor (TCR) and B-cell receptor (BCR). Their inhibition further suppresses T-cell receptor-driven activation and interferes with cytolytic effector functions of $CD8^+$ T cells and NK cells that contribute to follicular destruction in AA. This dual mechanism, blocking both cytokine-mediated activation through JAK3 and antigen-receptor-mediated cytotoxicity through TEC kinases, leads to a synergistic immunomodulatory effect that restores hair-follicle immune privilege and enables hair regrowth.

Importantly, ritlecitinib's high specificity for JAK3 distinguishes it from broader JAK inhibitors such as baricitinib or tofacitinib, which target JAK1 or JAK2 and are therefore more likely to affect hematopoiesis and lipid metabolism. By focusing on immune-restricted pathways, ritlecitinib may achieve effective suppression of the autoimmune response in AA while maintaining a more favorable systemic safety profile - an aspect of particular importance in children and adolescents, for whom long-term immunosuppression poses unique risks.

Acne

Acne is a common adverse effect of ritlecitinib in adults and adolescents with alopecia areata, with incidence rates ranging from 10.4% to 13% in pivotal phase 2b/3 trials and integrated safety analyses.[1-4] Meta-analyses confirm a statistically significant increased risk of acne with ritlecitinib compared to placebo (odds ratio [OR] 2.6, 10.4% vs 4.3%).[4-5] Compared to other JAK inhibitors, ritlecitinib's acne risk is similar to deuruxolitinib (13.6%) and lower than baricitinib (up to 18.2%).[4][6] Acne is generally mild and does not frequently lead to treatment discontinuation.[2-3] However, in some cases, acne may impact adherence or quality of life, particularly in adolescents, where psychosocial effects of skin changes are more pronounced.[2-3][7]Acne typically develops within the first 8–12 weeks of ritlecitinib therapy, often during the initial loading dose period (200 mg daily for 4 weeks, followed by 50 mg daily maintenance).[1-2][8-9] Most cases are mild to moderate, presenting as papulopustular eruptions on the face, chest, or back. Severe or nodulocystic acne is rare. There is no clear difference in acne presentation between adults and adolescents, although adolescents may report higher distress and impact on self-image.[3][9]Baseline skin assessment is recommended prior to initiating ritlecitinib, with documentation of pre-existing acne or other dermatologic conditions.[1-2] Ongoing monitoring should include regular skin examinations at each follow-up visit, with grading of acne severity using standardized scales (e.g., Investigator's Global Assessment or Leeds Acne Grading System).[1-2] Progression or complications such as scarring, secondary infection, or significant psychosocial distress should

be documented. Patient education is essential: patients should be instructed to self-monitor for new or worsening acne and report promptly, especially if lesions are painful, extensive, or associated with systemic symptoms.[1-3] Management of acne during ritlecitinib therapy should follow evidence-based dermatologic guidelines. Mild cases can be treated with topical agents (benzoyl peroxide, topical retinoids, or topical antibiotics). Moderate cases may require combination topical therapy or oral antibiotics (e.g., doxycycline), with consideration of the patient's age and comorbidities.[2-3][10] Severe or refractory cases may warrant referral to dermatology and consideration of systemic therapy. Dose interruption or discontinuation of ritlecitinib is rarely required; it should be considered only if acne is severe, unresponsive to standard therapy, or significantly impairs quality of life.[1-2] Multidisciplinary care may be appropriate for adolescents with significant psychosocial impact.

Headache

Headache is a common adverse effect in adults and adolescents receiving ritlecitinib for alopecia areata, with incidence rates ranging from 10.8% (during 24-week placebo-controlled periods) up to 20.8% in long-term extension studies.[1-7] Meta-analyses and real-world pharmacovigilance data confirm headache as one of the most frequently reported adverse events, with a reporting odds ratio of 3.22 in the FDA Adverse Event Reporting System.[8] Headache is typically mild to moderate in severity and occurs at a slightly higher rate than placebo (8.5–10.6%).[1][4][7]

Headache most often presents early in the course of ritlecitinib therapy, frequently during the initial 4-week loading dose (200 mg daily), but can also occur during maintenance dosing (50 mg daily).[3-4] There is no clear difference in headache rates or severity between adults and adolescents, although adolescents may be more likely to report headache as impacting daily activities.[3][6] Severity is generally graded as mild (not interfering with activities) or moderate (requiring occasional analgesics), and severe headache is rare, with very few cases leading to dose interruption or discontinuation.[2-3]

When compared to other JAK inhibitors, the risk of headache with ritlecitinib is similar to baricitinib (6.1%), brepocitinib (10.6%), and lower than deuruxolitinib (21.4%).[7] Odds ratios for headache versus placebo are modest (OR 1.2 for ritlecitinib), indicating no major safety signal relative to other agents in this class.[7] Evaluation of headache in patients receiving ritlecitinib should include a baseline assessment of headache history and risk factors (e.g., migraine, tension-type headache, medication overuse). During treatment, regular monitoring of headache frequency, severity, and impact on function is recommended at each follow-up visit, using standardized scales such as the Numeric Rating Scale or Headache Impact Test. If headache is persistent, severe, or associated with neurological symptoms (e.g., visual changes, focal deficits), further evaluation and consideration of dose adjustment or discontinuation may be warranted.[2-4] In clinical trials, permanent discontinuation due to headache is rare (<1%).[2-3] Management of headache during ritlecitinib therapy is primarily supportive. First-line interventions include non-opioid analgesics (acetaminophen, NSAIDs), hydration, sleep hygiene, and stress reduction. Patient education regarding the benign nature of most headaches and self-monitoring for escalation is important. Neurology referral should be considered for refractory, severe, or atypical headache presentations, or if secondary causes are suspected.[2-4][6] Most cases resolve spontaneously or with minimal intervention.

Nasopharyngitis and upper respiratory tract infections

Across multiple randomized controlled trials and integrated safety analyses, these events are among the most frequently reported adverse effects, with nasopharyngitis occurring in 10–14% and upper respiratory tract infections in 10–15% of patients receiving ritlecitinib, compared to 6% for nasopharyngitis and similar rates for upper respiratory tract infections in placebo groups.[2-6]

Most cases are mild to moderate in severity, self-limited, and do not require interruption or discontinuation of therapy. The incidence is dose-dependent, with higher rates observed in patients receiving a 200 mg loading dose followed by 50 mg daily maintenance.[2-3] Serious infections are rare, with no increase in serious infection rates compared to placebo, and no cases of opportunistic infection, major adverse cardiovascular events, or deaths attributable to these respiratory events have been reported in either adult or adolescent populations.[3][5-6]

Pyrexia

In addition to routine monitoring for fever, evaluation of pyrexia in adults and adolescents receiving ritlecitinib should incorporate assessment of the temporal relationship to drug initiation, as pyrexia is most frequently observed during the first months of therapy and is reported in up to 13% of patients in long-term studies.[2] Clinical trial data indicate that most cases are mild, self-limited, and do not require dose interruption or discontinuation.[2-3] However, because ritlecitinib is an immunomodulator, any episode of pyrexia warrants careful evaluation for underlying infection, including history, physical examination, and targeted laboratory or microbiological investigations if clinically indicated.[3-4]

If pyrexia is accompanied by other symptoms such as cough, sore throat, or localized pain, further workup for respiratory or urinary tract infection should be considered, as these are among the most common infectious adverse events in this population.[3-4] Persistent or recurrent pyrexia, or pyrexia associated with systemic symptoms (e.g., rigors, hypotension), should prompt consideration of dose interruption and escalation of diagnostic evaluation to exclude serious or opportunistic infection.[2-3] In long-term extension studies, the rate of serious infection remains low, and most cases of pyrexia resolve without sequelae.[2]

Patient education regarding prompt reporting of fever and associated symptoms is recommended, and clinicians should maintain a low threshold for investigation in patients with additional risk factors for immunosuppression or comorbidities. Overall, the evaluation of pyrexia in ritlecitinib-treated patients should be systematic, with a focus on early detection of infection and minimizing unnecessary treatment interruption.[2-4]

Folliculitis

Folliculitis should be evaluated as a potential adverse effect in adults and adolescents receiving ritlecitinib for alopecia areata, by performing regular skin examinations at baseline and during follow-up, with particular attention to new or worsening pustular or papular lesions on the scalp, face, or body. The incidence of folliculitis in clinical trials was 3.1% with ritlecitinib 50 mg, slightly higher than placebo (1.9%), and rates were higher in groups receiving a 200 mg loading dose followed by 50 mg daily maintenance.[1-2] Most cases were mild to moderate and did not require dose interruption or discontinuation.[1-2] Evaluation should include documentation of lesion morphology, distribution, severity, and associated symptoms (pain, pruritus, erythema, or drainage). Assessment for secondary infection or abscess formation is warranted if lesions are extensive or accompanied by systemic symptoms. In the absence of severe or complicated folliculitis, management is typically supportive, with topical antiseptics or antibiotics as first-line therapy. Persistent, severe, or recurrent cases may require oral antibiotics or dermatology referral. Dose interruption or discontinuation of ritlecitinib is rarely necessary and should be reserved for refractory or complicated cases.[1-2]

Urticaria

Evaluation of urticaria as a potential adverse effect in adults and adolescents receiving ritlecitinib for alopecia areata, should include ongoing surveillance for cutaneous hypersensitivity reactions throughout the course of therapy, as urticaria was reported at higher rates in patients receiving higher ritlecitinib doses (notably the 200 mg loading dose plus 50 mg maintenance) compared to placebo in phase 2b/3 and long-term studies.[2-4] Real-world pharmacovigilance data confirm a positive safety signal for urticaria, with a reporting odds ratio of 6.02, indicating a statistically significant association with ritlecitinib exposure.[5] When urticaria is suspected, clinicians should document the temporal relationship to drug initiation, distribution and morphology of lesions, and any associated systemic symptoms such as angioedema or respiratory compromise. It is important to distinguish urticaria from other dermatologic adverse events (e.g., drug hypersensitivity, folliculitis, or atopic dermatitis), as management and risk stratification differ. For mild cases, supportive therapy with non-sedating antihistamines is recommended; moderate or severe cases, or those with systemic involvement, may require dose interruption and further evaluation for alternative etiologies or coexisting hypersensitivity syndromes.[2-3][5] Persistent or recurrent urticaria warrants consideration of dermatology referral and, in rare cases, discontinuation of ritlecitinib. Long-term safety analyses indicate that most cases are self-limited and do not result in permanent discontinuation, but vigilance is required for escalation to more severe hypersensitivity reactions.[3][6]

Urinary tract infection

Urinary tract infection should be evaluated as a potential adverse effect in adults and adolescents receiving ritlecitinib for alopecia areata by monitoring for new onset of urinary symptoms (dysuria, frequency, urgency, suprapubic pain, or hematuria) at each follow-up visit, especially in the first 24 weeks of therapy when incidence is highest.[1] The risk is dose-dependent, with higher rates observed in patients receiving a 200 mg loading dose followed by 50 mg daily maintenance, but most cases are mild to moderate and do not require discontinuation.[1]

Evaluation should include a focused history and physical examination to distinguish uncomplicated lower urinary tract infection from complicated or upper tract involvement. Urinalysis and urine culture are recommended for symptomatic patients to confirm infection and guide therapy. If urinary tract infection is confirmed, standard antimicrobial treatment should be initiated according to local resistance patterns. Persistent, recurrent, or severe infections warrant consideration of dose interruption and further investigation for underlying risk factors, including immunosuppression or anatomical abnormalities.

Herpes zoster infection

The incidence of herpes zoster infection in adults and adolescents receiving ritlecitinib for alopecia areata is 1.5% (0.9 per 100 patient-years) in integrated analyses of clinical trial data, with a median exposure of 624 days and a total of 2091.7 patient-years of follow-up.[1] In the pivotal phase 2b/3 trial, eight cases of herpes zoster were reported among ritlecitinib-treated patients (one in the 200 mg + 50 mg group, two in the 200 mg + 30 mg group, and five in the 50 mg group); none were serious and all resolved without sequelae.[2] In the long-term open-label extension (mean exposure ~2 years), six cases of herpes zoster were reported among 449 patients, again with no serious or disseminated cases.[3]

No cases of herpes zoster were reported in the adolescent-only subgroup through 48 weeks of treatment.[4] All reported cases in adults and adolescents were localized, mild to moderate in severity, and did not require permanent discontinuation of ritlecitinib.[1-3] There were no cases of multi-dermatomal, disseminated, or ophthalmic herpes zoster, and no opportunistic or life-threatening presentations were observed.[1][3]

Serious adverse events

Building on the drug label data, recent clinical trials and integrated safety analyses provide further granularity regarding the rates and types of serious adverse events in adults and adolescents receiving ritlecitinib for alopecia areata. In the largest integrated analysis (n = 1294; 2091.7 patient-years), serious adverse events occurred in 4.4% of patients (57/1294), with permanent discontinuation due to adverse events in 6.0% (78/1294). [2]

Malignancy (excluding nonmelanoma skin cancer) was reported in 0.5% of patients (0.3 per 100 patient-years), with three cases observed in a 24-month open-label extension (all breast cancer; two considered unrelated to treatment, one possibly related).[3] Major adverse cardiovascular events occurred in 0.2% of patients (0.1 per 100 patient-years), with three events (including one pulmonary embolism and two other cardiovascular events) reported in long-term follow-up.[2-3] Opportunistic infections were rare, occurring in less than 0.1% of patients (0.05 per 100 patient-years), with only two cases identified (multi-dermatomal herpes zoster) and no cases of tuberculosis, pneumocystis, or other classic opportunistic pathogens.[2]

Serious infections (including appendicitis, diverticulitis, empyema, and sepsis) were reported in 0–3.2% of ritlecitinib-treated patients in placebo-controlled cohorts, similar to placebo (1.9%).[2][4] In long-term studies, four serious infections were observed among 449 patients over 24 months.[3] No deaths, major cardiovascular events, or opportunistic infections were reported in adolescent subgroups up to 48 weeks.[5]

Comparative safety profile of ritlecitinib versus other oral JAK inhibitors in alopecia areata

The safety profile of ritlecitinib compares favorably to other oral Janus kinase (JAK) inhibitors approved for alopecia areata, including baricitinib, deuruxolitinib, and brepocitinib. Across randomized controlled trials and meta-analyses, ritlecitinib 50 mg daily is associated with a lower or similar incidence of common adverse effects such as headache (12.5–17.7%), acne (10.4%), nasopharyngitis (12.4%), and upper respiratory tract infections (10–15%) compared to other JAK inhibitors.[1-4]

Baricitinib is more likely to cause acne (up to 18.2%), urinary tract infections (7.3%), and hyperlipidemia (18.2%) than ritlecitinib, with similar rates of headache and upper respiratory tract infections.[2-3][5] Deuruxolitinib demonstrates a higher overall rate of adverse events, particularly headache (21.4%) and

acne (13.6%), and is more likely to cause elevated creatine phosphokinase.[1-3] Brepocitinib is associated with higher rates of elevated creatinine (27.7%) and upper respiratory tract infections (23.4%).[3]

Serious adverse events, including malignancy (0.5%), major adverse cardiovascular events (0.2%) and opportunistic infections (<0.1%), are rare and occur at similar rates across all oral JAK inhibitors, with no significant increase compared to placebo.[3-4] Discontinuation due to adverse events is infrequent for ritlecitinib (6–6.5%) and comparable to other agents.[4][6] In summary, ritlecitinib exhibits a favorable safety profile relative to other oral JAK inhibitors for alopecia areata, with lower rates of certain adverse effects and a comparable risk of serious events.[1-5]

Conclusions.

Ritlecitinib is an effective and generally well-tolerated oral treatment for adolescents and adults aged ≥12 years with alopecia areata. Across clinical trials and long-term extension studies, the most common adverse effects include headache, acne, and nasopharyngitis, with additional events such as upper respiratory tract infections, folliculitis, urticaria, pyrexia, dizziness, and urinary tract infections occurring less frequently. These reactions are typically mild to moderate and seldom require treatment interruption. Laboratory abnormalities - such as transient decreases in hemoglobin and in neutrophil, lymphocyte, and platelet counts - tend to stabilize with continued therapy and rarely lead to clinically relevant consequences.

Serious adverse events, including malignancies, major cardiovascular events, and severe or opportunistic infections, are uncommon and occur at rates similar to placebo. No deaths, disseminated infections, or severe hypersensitivity reactions have been reported in studies up to 24 months, including among adolescents.

Compared with other oral JAK inhibitors used in alopecia areata, ritlecitinib demonstrates a favorable or comparable safety profile, with lower incidence of specific events such as acne, headache, and lipid abnormalities. Its selective inhibition of JAK3 and TEC kinases may contribute to reduced systemic toxicity, making it a suitable option for long-term management, particularly in younger patients.

Overall, current evidence supports the safety and tolerability of ritlecitinib for prolonged use in adolescents and adults with moderate-to-severe alopecia areata. Continued post-marketing surveillance will help refine the long-term risk assessment, especially in pediatric populations.

Disclosure

Author's contribution:

Conceptualization and Methodology: AK, AD, DW; Software: Not applicable; Check: IG, PH, WEN; Formal analysis: AK, AB, AM; Investigation: AD, DW, LJ; Resources: Not applicable; Writing - rough preparation: AK, PH, KJ; Writing - review and editing: KJ, IG, WEN; Supervision: AK, AM, DW; Project administration: AK.

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