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Research Article

Post-Marketing Safety Profile of Ritlecitinib: A Disproportionality Analysis Based on the FDA Adverse Event Reporting System (FAERS) Database

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Abstract

Background: This study aimed to investigate the adverse events (AEs) associated with ritlecitinib using data from the United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), thereby providing real-world evidence to support safer clinical use and inform future research. **Methods:** A retrospective pharmacovigilance analysis was conducted using FAERS data from the third quarter of 2023 to the fourth quarter of 2025. Disproportionality analysis was used to detect AE signals using four established methods: reporting odds ratio, proportional reporting ratio, Medicines and Healthcare Products Regulatory Agency criteria, and Bayesian confidence propagation neural network. AEs identified by all four methods were defined as positive risk signals. **Results:** Of the 3180 AE reports with ritlecitinib as the primary suspected drug, 66 kinds of AEs of Preferred Term level met the criteria for positive signal detection. Of these, 42 were not included in the current product label. The most frequently reported risk signals included drug ineffective, therapeutic product effect incomplete, condition aggravated, headache, urticaria and acne. Risk signals were predominantly clustered in the System Organ Classes of skin and subcutaneous tissue disorders, investigations, and general disorders and administration site conditions. **Conclusions:** These findings highlight the importance of continued pharmacovigilance and early clinical intervention to mitigate safety risks during routine use.

Keywords: ritlecitinib; alopecia areata; pharmacovigilance; drug-related side effects and adverse reactions; Janus kinase inhibitors; adverse drug reaction reporting systems

1. Introduction

Alopecia areata (AA) is an autoimmune disorder affecting hair follicles that typically presents as non-scarring, patchy hair loss, and potentially progresses to alopecia totalis or alopecia universalis in severe cases [1]. AA may develop at any age, although it predominantly affects young adults with a lifetime incidence of approximately 2%. This condition significantly affects patients' quality of life and mental well-being [2,3]. Conventional therapies, such as glucocorticoids, minoxidil, and immunosuppressants, are often characterized by delayed onset and variable efficacy, and moderate-to-severe AA has historically been difficult to manage [4].

Although the precise pathogenesis of AA is not yet fully elucidated, emerging evidence implicates the loss of immune privilege in hair follicles, immune cell activation, and dysregulation of immunity [5,6]. Evidence suggests that increased IL-15 levels in the outer root sheath activate the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway via the IFN-γ receptor, thereby upregulating $CD8^+$ cytotoxic T cells. This immune response can enhance inflammation, leading to hair follicle destruction. JAK inhibitors block JAK-STAT signaling to reduce the activation of $CD8^+$ cytotoxic T cells, thereby halting AA development [7,8]. Ritlecitinib is an oral, selective inhibitor of Janus kinase 3 (JAK3) and TEC family kinases, approved for the treatment of severe alopecia areata (AA) in adults and adolescents aged 12 years and older. It received regulatory approval from the United States Food and Drug Administration (FDA) in June 2023, followed by authorization in the European Union and China [9]. By inhibiting both JAK3 and TEC kinase family members, ritlecitinib selectively disrupts JAK/STAT pathway, thereby facilitating hair regrowth [10]. Clinical trials have demonstrated its efficacy across various dermatological and immune-related conditions [11,12]. Nevertheless, the FDA has issued a black box warning for ritlecitinib, citing the risks of serious infections, malignancy, major cardiovascular adverse events (AEs), thrombosis, and mortality [13]. In a randomized, double-blind, multicenter, phase 2b–3 trial involving 718 participants, 76–86% reported AEs, and three treatment-related serious AEs were observed: empyema, sepsis, and breast cancer [11]. A separate subgroup analysis of Asian patients with AA (n = 186) revealed AE rates ranging from 70.6% to 89.3%, including

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audiological disturbances and reductions in specific haematological parameters [14].

Despite promising clinical trial results regarding efficacy, long-term safety data on ritlecitinib remain limited, particularly across diverse ethnic populations and real-world settings. There is also a paucity of data on the use of ritlecitinib in paediatric patients under 12 years of age, older adults, and individuals with comorbid autoimmune or cardiovascular conditions. Given the high frequency of AEs reported in clinical trials and the potential for rare but serious complications, robust post-marketing pharmacovigilance studies are urgently needed to characterise the safety profile of ritlecitinib in routine clinical practice. This study aimed to investigate the AEs associated with ritlecitinib using data from the United States FDA Adverse Event Reporting System (FAERS), providing real-world evidence to support safer clinical use and inform further research.

2. Materials and Methods

2.1 Study Design and Data Source

This retrospective pharmacovigilance study employed disproportionality analysis using data from FAERS. FAERS is a publicly accessible global database that collects spontaneous AE reports, making it a valuable source for real-world pharmacovigilance studies [15]. The FAERS dataset comprises seven types of files: adverse drug reaction (ADR) information, demographic and administrative information, drug information, indication for use, patient outcomes, reporting sources, and therapeutic start and end dates [16]. The AE reports submitted between the third quarter of 2023 and the fourth quarter of 2025 (ten quarters in total) were included. The authors had no access to information that could identify individual participants during or after data collection. Our study adhered to the REporting of A Disproportionality Analysis for DrUg Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance (READUS-PV) requirements [17].

2.2 Data Processing

FAERS data for the target period were imported into MySQL (version 8.0.26, Oracle Corporation, Redwood City, California, USA) for processing. Following FDA guidelines, duplicate records were excluded by retaining entries with the most recent "FDA_DT" (FDA receipt date) for each unique "PRIMARYID". When "FDA_DT" and "CASEID" were identical, the record with the higher "PRIMARYID" was retained. Reports identifying ritlecitinib as the primary suspect (PS) drug were extracted using both its generic name ("ritlecitinib") and brand name ("LITFULO") as keywords. Demographic details, reporting sources, AEs, indications, and outcomes were also collected. Only AEs reported in at least three individual cases were included in the signal-detection process. All AE terms were standardized using the Preferred Terms (PTs) of the Medical Dictionary for Regulatory Activities (MedDRA), version 28.0, and categorized according to the System Organ Class (SOC) hierarchy.

2.3 Statistical Analysis

Four established algorithms of disproportionality analysis were conducted to identify AE signals in this study: reporting odds ratio (ROR), proportional reporting ratio (PRR), Medicines and Healthcare Products Regulatory Agency (MHRA) method, and Bayesian confidence propagation neural network (BCPNN). The calculations were based on a 2 × 2 contingency table (Table 1). Signal detection thresholds were defined as follows: ROR, number of reports (a) ≥3, and lower 95% confidence interval (CI) >1; PRR: a ≥3 and lower 95% CI >1; MHRA: a ≥3, PRR ≥2, and $\chi^2 \geq 4$; BCPNN: information component-2 standard deviation (IC-2SD) > 0. AEs that met the criteria for all four algorithms were defined as positive risk signals. In addition, we identified unexpected AE signals, defined as statistically significant AEs that were not listed on the approved drug label. Data analysis was performed using SPSS Statistics (version 26.0, IBM, Armonk, New York, USA) and Excel (version 2021, Microsoft Corporation, Redmond, Washington, USA). Time of onset was determined as the interval between "START_DT" (start date for ritlecitinib use) and "EVENT_DT" (date of AE occurrence). Error reports with inaccurate dates, or for which "START_DT" fell before the market approval date or after "EVENT_DT", were excluded. The time-to-onset was described by median and interquartile range (IQR).

Table 1. 2 × 2 Contingency table for disproportionality analysis.

Drug	Number of targeted AE reports	Number of other AE reports
Targeted drug	a	b
Other drugs	c	d

Note: a represents the number of reports of the target adverse event (AE) associated with the target drug; b represents the number of reports of other AEs associated with the target drug; c represents the number of reports of the target AE associated with non-target drugs; d represents the number of reports of other AEs associated with non-target drugs.

3. Results

3.1 Baseline Characteristics

In total, 14,326,129 AE reports were extracted from the FAERS database. Following data processing, 3180 reports identified ritlecitinib as a primary suspect drug. Among these, 203 of 570 AE types had three or more reports, amounting to 2705 AE reports. The data-processing workflow is illustrated in Fig. 1.

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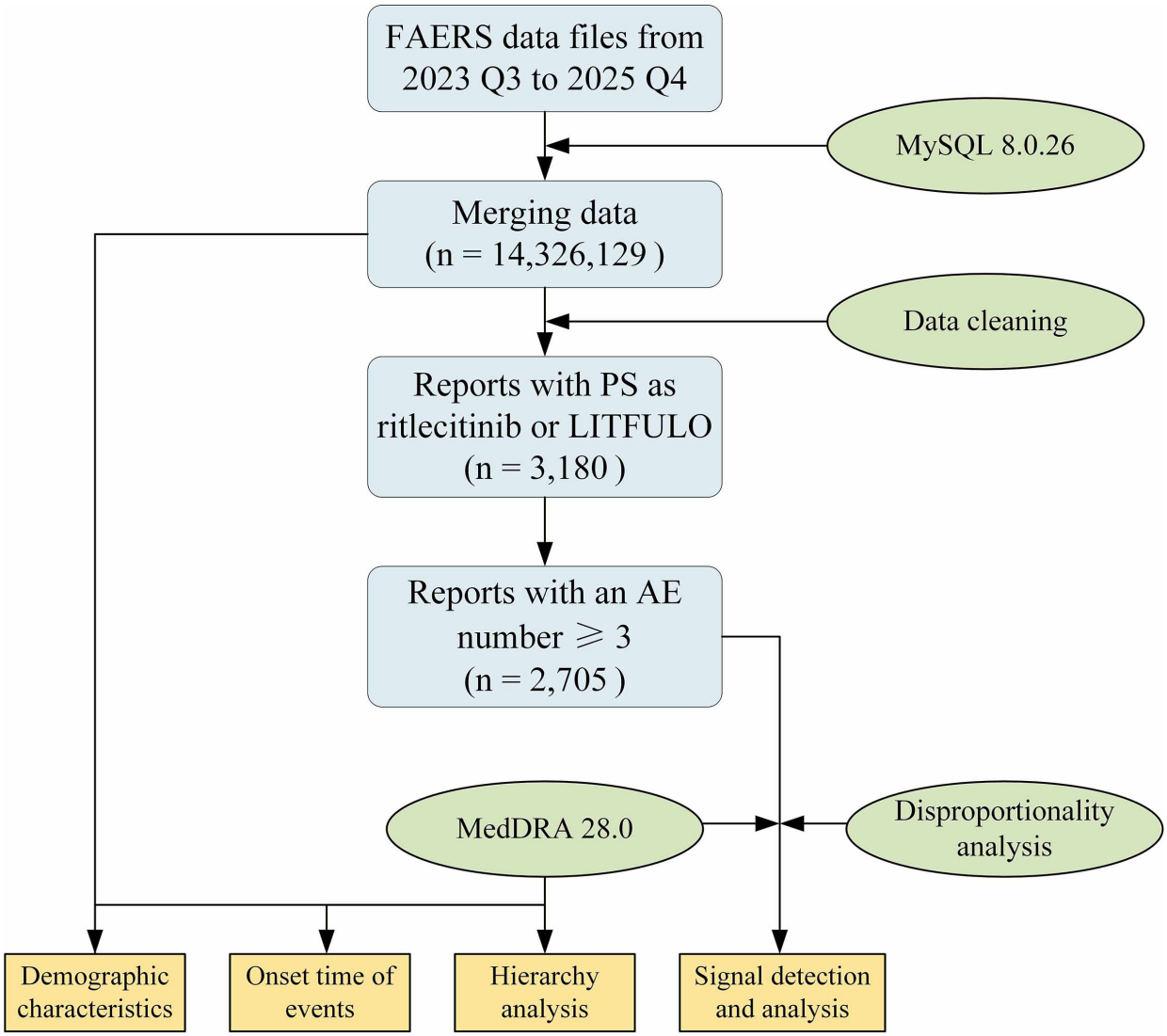


Fig. 1. The process of ritlecitinib-associated AEs from the FAERS database. AE, adverse event; FAERS, Food and Drug Administration Adverse Event Reporting System; MedDRA, Medical Dictionary for Regulatory Activities; PS, primary suspect.

Of the 3180 reports, sex was reported as female in 1096 (34.5%) and male in 572 (18.0%), while sex information was unavailable in 1512 (47.5%) reports. The youngest reported patient was a 7-year-old male, and the oldest was an 84-year-old female. Regarding age distribution, most reports involved adults (n = 829, 26.1%), followed by adolescents (n = 432, 13.6%); older patients were reported less frequently (n = 136, 4.3%). The most commonly reported PT among patients under 12 years of age was off-label use (n = 14, 87.5%), whereas for patients in other age groups, it was drug ineffective (group 12–17 years old [n = 75, 17.4%], group 18–64 years old [n = 127, 15.3%], group ≥65 years old [n = 26, 19.1%]). Health care professionals submitted 1199 reports (37.7%). The United States was the most frequently reported country, contributing 1737 reports (54.6%). The outcome data were largely incomplete, with 2863 reports (90.0%) missing this information. Among the available outcomes, 2 cases reported death, yet one of these was documented as a completed suicide. Detailed demographic characteristics are summarized in Table 2. In addition, 20 reports listed diagnoses other than AA as the sole indication, including atopic dermatitis, psoriasis, vitiligo, arthritis, pemphigus, and hypothyroidism, all of which reported "off-label use" as an AE. Moreover, a 54-year-old female with hypothyroidism reported weight decreased, and a 14-year-old male with psoriasis reported bronchitis.

3.2 Signal Detection Results for AEs

The distribution of ritlecitinib-associated AEs at the SOC level is shown in Fig. 2. The top six SOCs were: general disorders and administration site conditions (n = 907, 28.5%); skin and subcutaneous tissue disorders (n = 437, 13.7%); injury, poisoning, and procedural complications (n = 294, 9.2%); investigations (n = 271, 8.5%); gastrointestinal disorders (n = 236, 7.4%) and infections and infestations (n = 236, 7.4%). At the PT level, the ten most frequently re-

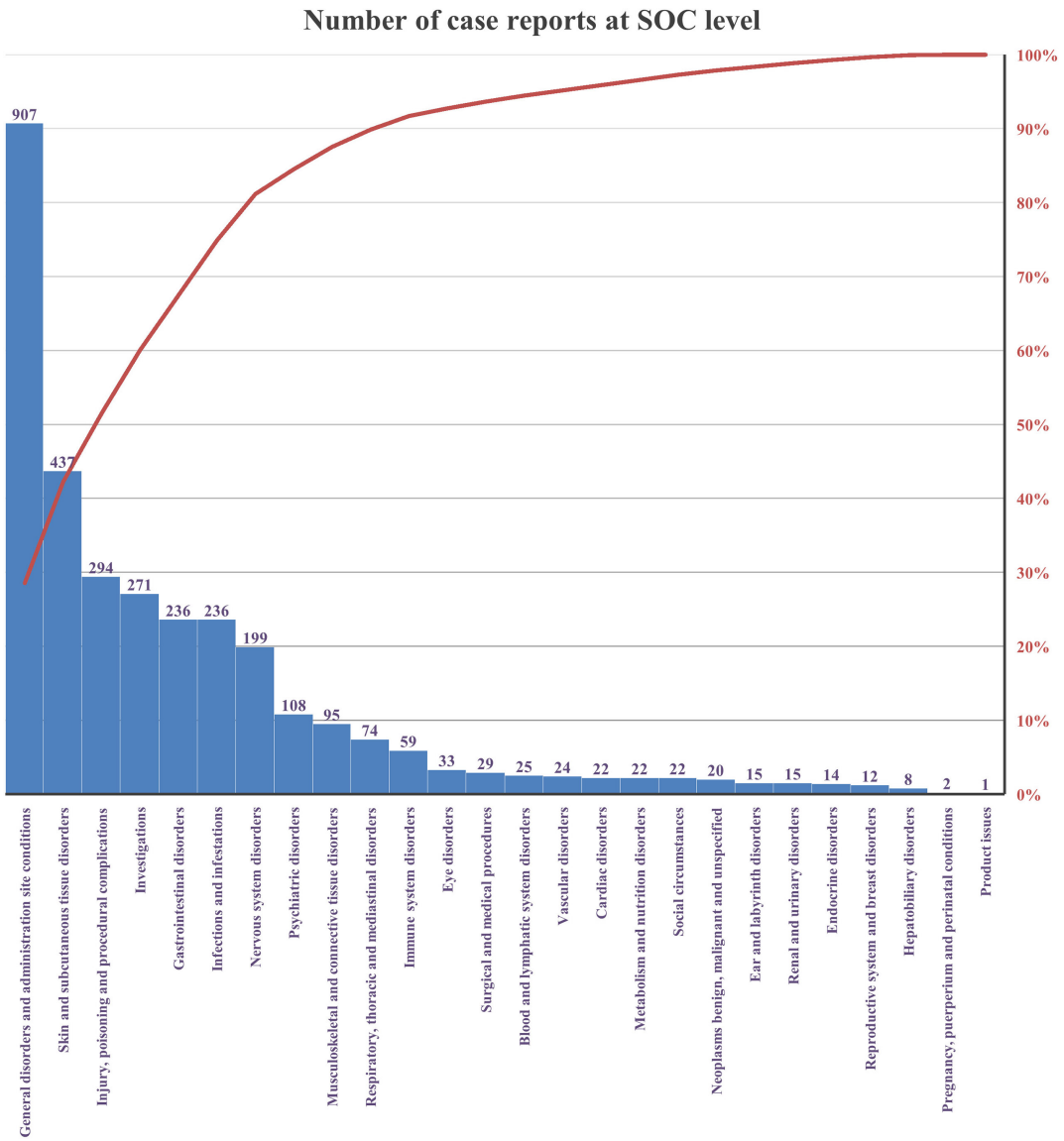


Fig. 2. The number of case reports for ritlecitinib-associated AEs at SOC level. AE, adverse event; SOC, System Organ Class.

ported AEs were: drug ineffective (n = 335, 10.5%), therapeutic product effect incomplete (n = 153, 4.8%), condition aggravated (n = 110, 3.5%), off-label use (n = 103, 3.2%), headache (n = 89, 2.8%), alopecia (n = 67, 2.1%), product dose omission issue (n = 67, 2.1%), diarrhea (n = 61, 1.9%), fatigue (n = 50, 1.6%) and pruritus (n = 48, 1.5%). Based on predefined criteria for positive risk signal detection, 66 kinds of AEs were identified as positive signals. Of these, 10 overlapped with AEs occurring at an incidence of ≥1% in the drug label, and 42 were new and unexpected (Table 3).

3.3 Onset Time of AEs

After data cleaning, onset time was reported in a total of 169 AE cases, with a median of 32 days (IQR 7–156 days) (Fig. 3). The onset of ritlecitinib-related adverse events varied widely, ranging from the day of administration to over a year later. Most cases, however, occurred within the first month after ritlecitinib initiation (n = 81, 47.9%).

4. Discussion

The current version of ritlecitinib's drug label includes safety concerns identified in clinical trials, but post-marketing data have not yet been described, and few published real-world studies are available. This pharmacovigilance study, based on a large dataset of spontaneous reports, analyzed AEs associated with ritlecitinib since its approval, identified potential unexpected AEs, and explored its off-label use. These findings provide valuable reference points for improving the safe use of these drugs in clinical practice.

Disproportionality analysis, establishing statistical associations between a given combination of drugs and AEs by comparing the observed and expected report numbers,

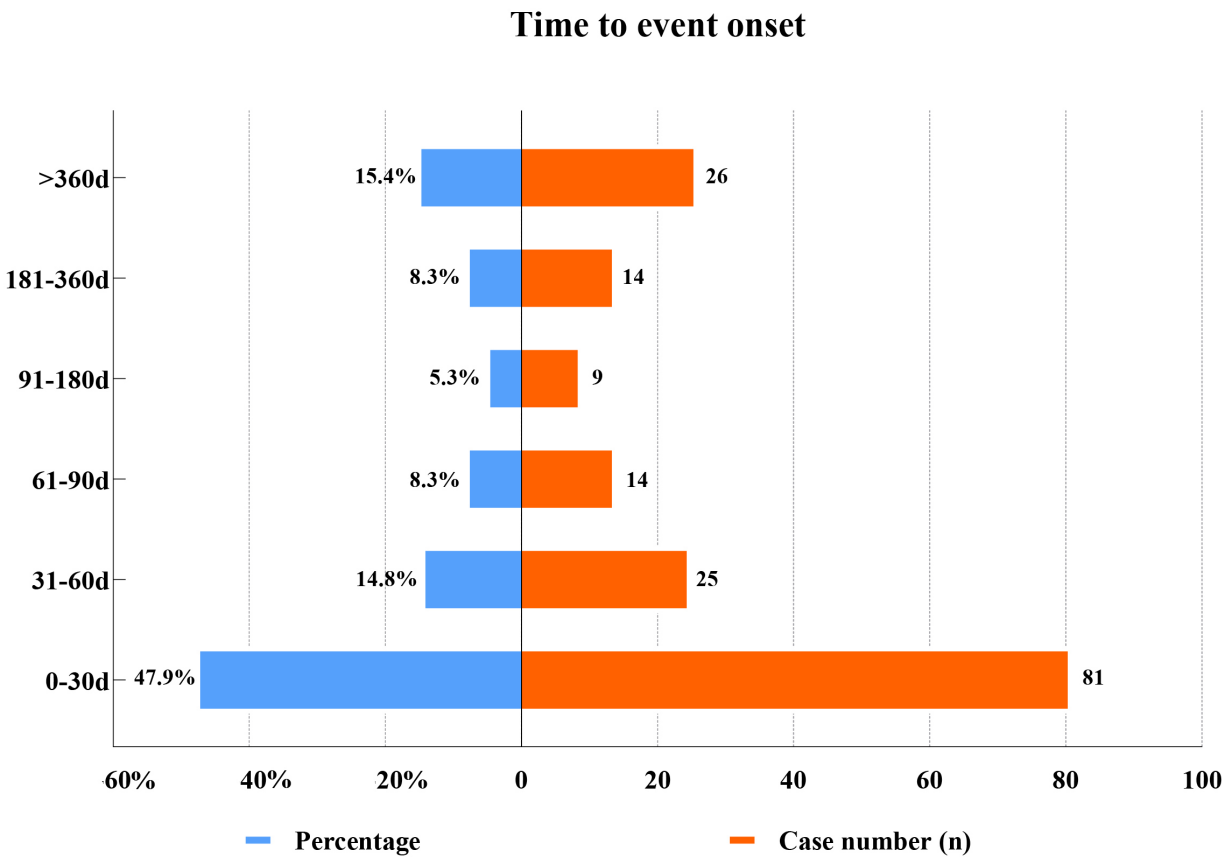


Fig. 3. Time to onset of ritlecitinib-associated AEs.

is a widely used analytical method in pharmacovigilance studies. It is currently irreplaceable for rapidly generating hypotheses concerning unpredictable and rare AEs [18]. Unfortunately, the varied mechanisms of disproportionality analysis methods may introduce bias into signal detection [19]. For example, while ROR and PRR are classical methods that are straightforward to calculate and interpret, their high sensitivity can lead to false positive signals [20]. To address this, we defined signals detected by all four of the disproportionality methods we employed as positive risk signals. This approach balances specificity, sensitivity, and consistency, thereby reducing the likelihood of false positive and false negative signals [21].

A 30-year epidemiological analysis of AA showed that both crude and age-standardized prevalence and incidence rates were approximately twice as high in females as in males, with bimodal peaks at ages 30–34 and 60–64 [22]. This may explain the higher proportion of female and adult cases in our dataset. While ritlecitinib is indicated for patients aged ≥12 years [9], we observed 16 reports in children under 12 years of age. Notably, 14 were derived from professional sources and reported off-label use as PT; 6 reported the drug ineffective, a positive risk signal identified in our analysis, demonstrating the clinical attention and safety concerns about unapproved pediatric use.

The United States accounted for the majority of the reports, likely due to the United States-based nature of FAERS and differences in market approval dates across countries. Notably, pharmacists contributed relatively few reports compared to physicians, highlighting the need to strengthen pharmacists' involvement in pharmacovigilance activities [23]. Despite the low proportion of serious outcomes, it remains to be seen whether this conclusion is valid, considering the significant lack of information.

Beyond AA, ritlecitinib has demonstrated efficacy and acceptable safety in the treatment of ulcerative colitis, Crohn's disease, vitiligo, and rheumatoid arthritis [9,24,25], which is partly reflected in the off-label indications reported here. Generally, hypothyroidism may lead to weight increase, but with limited information we were unable to determine whether the weight decrease reported in the aforementioned female patient with hypothyroidism was drug-induced [26]. Although off-label use may reveal new therapeutic avenues, it also presents safety risks that warrant close assessment [27].

We identified 24 positive signals consistent with the drug label, supporting the reliability of our analysis. All the positive signals were distributed across 13 SOC categories, with the majority falling under skin and subcutaneous tissue disorders (n = 18), investigations (n = 14), and general disorders and administration site conditions (n

Table 2. Demographic characteristics of AE reports with ritlecitinib as the PS in the FAERS database, from Q3 2023 to Q4 2025.

Characteristics	Report number (n)	Proportion (%)
Number of reports	3180	
Sex		
Female	1096	34.5
Male	572	18.0
Unknown	1512	47.5
Age (year)		
<12	16	0.5
12–17	432	13.6
18–64	829	26.1
≥65	136	4.3
Unknown	1767	55.5
Reports by occupation		
Consumer	638	20.1
Physician	598	18.8
Health-professional	565	17.8
Pharmacist	36	1.1
Unknown	1343	42.2
Reported countries		
United States	1737	54.6
Other countries	105	3.3
Unknown	1338	42.1
Outcomes		
Death	2	0.1
Life-threatening	4	0.1
Disability	3	0.1
Hospitalization	60	1.9
Other serious	248	7.8
Unknown	2863	90.0

AE, adverse event; FAERS, FDA Adverse Event Reporting System; PS, primary suspect; Q, quarter.

= 10). Although AA is the labelled indication, most risk signals also appear under the SOC of the skin and subcutaneous tissue disorders. After excluding overlapping or non-specific AEs, such as alopecia, alopecia totalis, dermatitis, rash, rash papular, skin lesion, and skin disorders, we still detected label-listed signals, including urticaria, allergic dermatitis, and acne. Recent studies have implicated the JAK pathway in chronic urticaria pathogenesis, suggesting that the urticaria signal observed here likely reflects acute rather than chronic presentations [28]. This mechanism may involve immunoglobulin E-mediated allergy, mast cell activation, or disruption of arachidonic acid metabolism [29]. Clinicians should monitor patients for cutaneous allergic reactions and determine whether the drug should be withdrawn promptly to avoid harming the patient and increasing the healthcare burden. Increased acne risk has also been reported with other JAK inhibitors in patients with AA and atopic dermatitis [30,31], potentially owing to immune response shifts, microbiome dysbiosis, and vulnerability to opportunistic infections [32]. Our study also identified other epidermal and dermal conditions (erythema multiforme and seborrhoeic dermatitis) and skin appendage conditions (hair color changes, hair texture abnormal, hair growth abnormal and madarosis) as potentially new and unexpected AEs, although the underlying mechanisms remain unclear.

Under the SOC of investigations, signals such as increased blood creatine phosphokinase, liver function test increased and lymphocyte count decreased were consistent with the known ADRs. JAK inhibitors may promote muscle development by reversing inflammation-mediated inhibition of myoblast differentiation, thereby increasing creatine phosphokinase levels [33]. To minimize risks, renal function should be monitored during clinical treatment to mitigate potential risks of muscle-related toxicity. Dose reduction or treatment delay should be considered when necessary. Liver enzyme elevations may result from ritlecitinib metabolism, particularly by transaminases [34]. Although dose adjustment is not routinely required for patients with moderate hepatic impairment (Child–Pugh B), regular monitoring for drug-induced liver injury is still recommended [35]. Previous studies have indicated that lymphocyte count exhibited an inverse relationship with age [36]. Consequently, elderly patients with ritlecitinib should be particularly attentive to the risk of lymphopenia, necessitating regular clinical monitoring of complete blood counts. Our study also identified blood pressure, cholesterol abnormalities, and elevated blood triglycerides as risk signals, although these are not yet listed on the drug label. Other JAK inhibitors, such as baricitinib and tofacitinib, have been linked to hypertensive urgency and hypercholesterolemia, supporting the clinical relevance of our findings and indicating the necessity of regular clinical monitoring of serum lipids and cholesterol levels, as well as blood pressure fluctuations, in patients receiving ritlecitinib [37].

A total of 10 risk signals classified under the SOC of general disorders and administration site conditions were identified, none of which were included in the current drug label. However, most were subjective evaluations of efficacy (e.g., drug ineffective, therapeutic product effect incomplete, condition aggravated) rather than safety concerns. Discrepancies between physician and patient assessments of treatment effectiveness are common in AA [38], and drug efficacy was not the focus of this study. Thus, these signals should be interpreted cautiously.

Diabetes mellitus and thyroid disorders were also detected as unexpected AEs. Dysregulation of the JAK/STAT pathway has been associated with metabolic disorders, including diabetes and obesity [39]. However, to date, no thyroid AEs have been definitively attributed to JAK inhibitors. Nevertheless, it remains essential to closely monitor blood glucose levels and thyroid function in ritlecitinib-receiving patients.

Table 3. Risk signal detection results for ritlecitinib-associated AEs at the PT level.

Serial No.	AE	Case number (n)	ROR method		PRR method		MHRA method (χ^2)	BCPNN
			ROR	95% CI	PRR	95% CI		IC-2SD
1	Drug ineffective	335	6.76	6.04–7.57	6.15	5.50–6.89	1463.45	2.42
2	Therapeutic product effect incomplete	153	26.70	22.69–31.43	25.47	21.64–29.97	3558.77	4.21
3	Condition aggravated	110	5.16	4.26–6.24	5.01	4.14–6.06	351.35	4.82
4	Headache*#	89	3.15	2.55–3.89	3.09	2.51–3.82	125.02	1.28
5	Alopecia	67	8.26	6.49–10.53	8.11	6.37–10.33	410.91	2.52
6	Urticaria*#	48	5.83	4.38–7.75	5.75	4.32–7.65	183.97	1.97
7	Acne*#	43	18.61	13.77–25.16	18.38	13.59–24.84	686.91	3.27
8	Blood creatine phosphokinase increased*#	35	37.45	26.80–52.33	37.05	26.52–51.76	1182.49	3.72
9	Infection*	34	3.83	2.73–5.37	3.80	2.71–5.33	67.50	1.32
10	Illness	32	2.37	1.67–3.35	2.35	1.66–3.34	23.68	0.67
11	Alopecia areata	30	352.47	242.71–511.86	349.15	240.43–507.04	9345.21	4.30
12	Nasopharyngitis*	28	2.17	1.50–3.15	2.16	1.49–3.13	16.35	0.51
13	Therapeutic product effect decreased	24	6.97	4.66–10.42	6.92	4.63–10.35	115.73	1.90
14	Drug hypersensitivity*	21	2.65	1.73–4.07	2.64	1.72–4.05	19.81	0.68
15	Therapeutic response unexpected	18	10.89	6.85–17.31	10.83	6.81–17.22	150.64	2.17
16	Product prescribing error	16	7.76	4.75–12.69	7.73	4.73–12.64	87.02	1.76
17	Chest pain	16	2.24	1.37–3.65	2.23	1.36–3.64	9.67	0.35
18	Hepatic enzyme increased*	16	3.88	2.37–6.34	3.86	2.37–6.32	31.21	1.02
19	Blood cholesterol increased	16	6.00	3.67–9.81	5.98	3.65–9.77	61.37	1.50
20	Drug ineffective for unapproved indication	14	3.94	2.33–6.67	3.93	2.33–6.65	27.74	0.97
21	Migraine*#	13	2.41	1.40–4.16	2.41	1.39–4.15	9.32	0.35
22	Contusion	12	2.30	1.30–4.05	2.29	1.30–4.04	7.49	0.25
23	Intentional product misuse	12	3.08	1.75–5.44	3.08	1.75–5.43	14.87	0.60
24	Impaired quality of life	11	7.15	3.95–12.92	7.13	3.94–12.89	51.90	1.40
25	Quality of life decreased	11	17.55	9.70–31.75	17.49	9.66–31.65	154.34	2.04
26	Diabetes mellitus	10	3.27	1.76–6.08	3.26	1.76–6.07	13.51	0.56
27	Upper respiratory tract infection*	10	3.34	1.79–6.21	3.33	1.79–6.20	14.08	0.59
28	Loss of personal independence in daily activities	10	2.37	1.27–4.41	2.36	1.27–4.40	6.57	0.20
29	Liver function test increased*	10	6.05	3.25–11.27	6.04	3.24–11.24	37.11	1.18
30	Dermatitis	9	7.38	3.83–14.21	7.36	3.83–14.17	43.27	1.25
31	Thyroid disorder	8	9.60	4.80–19.24	9.58	4.78–19.19	53.12	1.33
32	Blood pressure abnormal	8	6.19	3.09–12.41	6.18	3.09–12.38	29.74	1.01
33	Folliculitis*#	8	5.56	2.78–11.13	5.55	2.77–11.11	25.42	0.92
34	Blood triglycerides increased	8	12.88	6.43–25.80	12.85	6.41–25.74	75.77	1.51
35	Disease recurrence	8	2.36	1.18–4.73	2.36	1.18–4.72	4.97	0.07
36	Herpes zoster*#	7	2.40	1.14–5.04	2.40	1.14–5.04	4.40	0.01
37	Madarosis	7	38.16	18.12–80.36	38.08	18.08–80.19	215.20	1.73
38	Emotional distress	7	3.12	1.49–6.56	3.12	1.48–6.55	8.06	0.28
39	Food allergy*	7	8.87	4.22–18.64	8.86	4.22–18.61	41.17	1.14

Table 3. Continued.

Serial No.	AE	Case number (n)	ROR method		PRR method		MHRA method (χ^2)	BCPNN
			ROR	95% CI	PRR	95% CI		IC-2SD
40	Lipids increased	7	61.83	29.31–130.47	61.70	29.24–130.18	354.66	1.82
41	Emotional disorder	7	5.11	2.44–10.75	5.11	2.43–10.73	19.19	0.73
42	Hair colour changes	7	20.56	9.78–43.23	20.51	9.75–43.14	110.66	1.55
43	Alanine aminotransferase increased*	7	2.90	1.38–6.09	2.90	1.38–6.08	6.90	0.20
44	Therapeutic product effect delayed	7	17.91	8.52–37.66	17.87	8.50–37.58	94.90	1.50
45	Tuberculosis*	7	12.50	5.95–26.27	12.48	5.94–26.22	62.70	1.33
46	Lymphopenia*	6	8.02	3.60–17.88	8.01	3.59–17.85	30.08	0.91
47	Dermatitis allergic*#	6	8.65	3.88–19.29	8.64	3.88–19.26	33.19	0.95
48	Skin disorder	6	3.27	1.47–7.29	3.27	1.47–7.28	7.31	0.21
49	Hepatitis B surface antibody positive*	6	381.34	165.62–878.06	380.63	165.31–876.41	1759.27	1.69
50	Skin lesion	6	3.90	1.75–8.69	3.90	1.75–8.68	10.18	0.37
51	Aspartate aminotransferase increased*	6	2.86	1.29–6.38	2.86	1.28–6.38	5.52	0.08
52	Rash papular*#	5	6.70	2.79–16.13	6.69	2.78–16.11	18.84	0.60
53	Blood cholesterol abnormal	5	19.23	7.98–46.31	19.20	7.97–46.24	68.73	1.07
54	Lymphocyte count decreased*	5	4.74	1.97–11.41	4.74	1.97–11.39	11.23	0.36
55	Skin irritation	5	3.58	1.49–8.61	3.58	1.49–8.60	6.88	0.14
56	Hair texture abnormal	4	15.06	5.64–40.21	15.04	5.63–40.16	39.19	0.69
57	Poor quality product administered	4	4.03	1.51–10.76	4.03	1.51–10.75	6.33	0.03
58	Swelling of eyelid	4	6.98	2.61–18.62	6.97	2.61–18.60	14.90	0.37
59	Hair growth abnormal	4	14.09	5.28–37.63	14.08	5.27–37.58	36.28	0.67
60	Alopecia totalis	4	439.97	157.50–1229.05	439.42	157.30–1227.51	1219.67	1.01
61	Erythema multiforme	3	8.33	2.68–25.88	8.33	2.68–25.85	12.68	0.11
62	Skin mass	3	7.48	2.41–23.21	7.47	2.41–23.19	10.95	0.07
63	Seborrhoeic dermatitis	3	28.18	9.05–87.72	28.15	9.04–87.64	53.42	0.41
64	Hepatitis B virus test positive*	3	175.65	55.40–556.93	175.48	55.34–556.41	347.06	0.53
65	Migraine with aura*#	3	26.42	8.49–82.22	26.39	8.48–82.14	49.80	0.40
66	Major depression	3	7.69	2.48–23.87	7.68	2.47–23.85	11.38	0.08

*AEs that are included in the drug insert. #Positive risk signals that overlap with adverse drug reactions occurring at ≥1% in the treated groups in the drug label.
AE, adverse event; BCPNN, Bayesian confidence propagation neural network; CI, confidence interval; IC-2SD, information component-2 standard deviation; MHRA, Medicines and Healthcare products Regulatory Agency; PRR, proportional reporting ratio; PT, Preferred Term; ROR, reporting odds ratio.

Mental health-related signals such as emotional distress and major depression were also observed under the SOC of psychiatric disorders. However, nearly 30% of patients with AA experience depression and 40% report anxiety symptoms [38]. An expert panel confirmed that psychosocial factors, alongside scalp hair loss, are key indicators of disease severity [40]. Therefore, it remains unclear whether ritlecitinib directly contributes to psychiatric events.

Moreover, we identified several infectious diseases, including folliculitis and herpes zoster, as risk signals, confirming the findings documented in the drug label. It is advisable to monitor patients for infection-related symptoms and signs during treatment with ritlecitinib. Importantly, however, we did not detect any signals for mortality, malignancy, major adverse cardiovascular events, or thrombosis — AEs that are also covered by the FDA's black box warning. These events may be rare and under-represented during spontaneous reporting.

We found that the median time to onset of ritlecitinib-related AEs was 32 days, and nearly half of the cases occurred within the first month of treatment. This indicated that we should pay particular attention to AEs occurring during the first month after ritlecitinib initiation. Early identification of drug-induced AEs can help alleviate patient discomfort and prevent potentially serious outcomes.

Currently, in addition to ritlecitinib, two other oral JAK inhibitors—baricitinib and deuruxolitinib—have been approved by the FDA for the treatment of adult patients with severe AA. Previous studies indicated that baricitinib-induced common AEs included acne, headache, and upper respiratory tract infections, which were largely consistent with the positive risk signals of ritlecitinib identified in our study. However, patients receiving baricitinib were reported to have elevated risks of venous thromboembolism and exacerbation of severe infections [7]. According to a network meta-analysis, deuruxolitinib may cause more AEs than other JAK inhibitors [8]. In comparison, ritlecitinib may serve as an optimal choice that balances efficacy and safety.

5. Limitations

First, due to the inherent nature of spontaneous reporting, data from FAERS inevitably introduce potential biases such as omissions, duplications, or even errors. These uncertainties may impact the reliability of the analysis and thus limit us from conducting stratified analyses by sex, age, and occupation. Second, we could not identify risk factors, accurately calculate the incidence of ritlecitinib-related AEs, or conduct comparative analysis owing to the absence of a control group and complete data. Third, since outcome data were missing for approximately 90% of the cases, we must acknowledge that this substantially limited our assessment of the AE severity to this drug. Fourth, disproportionality analysis is inherently limited in that it does not establish causality but rather statistical associations. No single disproportionality analysis method is definitively superior for detecting drug safety signals [41]. Similarly, a negative result does not rule out risk, nor should a lower-than-expected number of reports be viewed as protective [18]. Therefore, further research using large-scale real-world active surveillance and longitudinal monitoring is essential to validate these findings [42].

6. Conclusions

This disproportionality analysis provides real-world evidence of the adverse event risks associated with ritlecitinib and offers directions for future research. Clinicians should closely monitor patients for cutaneous changes and alterations in laboratory markers during treatment. Attention should also be paid to the emergence of potential adverse events. Early recognition and intervention are essential to minimize risks throughout the treatment course.

Availability of Data and Materials

All data were publicly accessed from "FDA Adverse Event Reporting System (FAERS): (https://www.fda.gov/drugs/surveillance/fdas-adverse-event-reporting-system-faers; accessed 25 October 2025)" and are freely available. The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

The conception and design of the study, the collection and analysis of data, and the first draft of the manuscript was written by MH. Analysis and validation of the data, as well as revision of the manuscript was performed by PL. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The FAERS database is publicly available and contains anonymized patient data. Because no identifiable personal information was used, ethical approval was not required. This was confirmed by the Ethics Committee of Chuiyangliu Hospital Affiliated With Tsinghua University.

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Conflicts of Interest

The authors declare no conflicts of interest.

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