

Treatment of Generalized Granuloma Annulare with JAK Inhibitors: Systematic Review

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Background: Granuloma annulare (GA) is a rare granulomatous skin condition characterized by well-demarcated, annular, erythematous to skin-colored plaques. Treating GA, particularly generalized GA (GGA), remains challenging due to the lack of FDA-approved therapies and limited large-scale studies. Traditional treatments, including corticosteroids, phototherapy, and systemic agents such as antimalarials and antibiotics, have shown variable efficacy. Recent research highlights the role of the JAK-STAT pathway in GA pathogenesis, leading to interest in JAK inhibitors as a potential treatment. Emerging evidence suggests that JAK inhibitors may reduce inflammation and lesion burden in GGA. This manuscript evaluates the efficacy and safety of JAK inhibitors in the treatment of GGA.

Results: Twenty-two studies were included, encompassing 50 patients with GGA. Agents included tofacitinib (n=27), baricitinib (n=11), upadacitinib (n=10), abrocitinib (n=1), and ruxolitinib (n=1). Across reports, most patients had recalcitrant disease with multiple prior treatment failures. Clinical improvement was observed in all patients, with complete response reported in 58.0% (29/50) and partial or near complete response in 42.0% (21/50). Median time to initial response was 5 weeks (IQR 2.75–8 weeks). Relapse occurred in a subset after discontinuation, but lesions often resolved with re-initiation. Adverse events were generally mild and consistent with known JAK inhibitor safety profiles (eg, hyperlipidemia, infections, herpes zoster).

Conclusion: JAK inhibitors show promise as a targeted therapy for GGA, offering a novel approach for patients with refractory disease. Further studies, including clinical trials, are needed to establish long-term efficacy and safety.

Keywords: granuloma annulare, generalized granuloma annulare, JAK inhibitors, JAK-STAT pathway, targeted therapy, granulomatous skin conditions

Introduction

Granuloma annulare (GA) is a rare granulomatous inflammatory skin condition characterized by annular, skin-colored to erythematous or violaceous plaques.¹ The localized form is the most common, appearing as isolated plaques, however approximately 15–25% of cases manifest as generalized GA (GGA), defined by at least 10 widespread annular plaques. Other variants include subcutaneous GA, commonly seen in children as firm, painless nodules; perforating GA, which presents with umbilicated papules that may drain fluid; and patch GA, characterized by erythematous patches, typically on the lower extremities.²

In the United States, the incidence of GA is approximately 0.04%, with a prevalence of around 0.06%. It is most frequently diagnosed in the fifth decade of life and is more common in women, with a female-to-male ratio of 3:1.³ GA is also more prevalent in Caucasians, occurring at up to twice the rate seen in Hispanic and Asian populations.

Several studies have explored the association between GA and various comorbidities. A large cohort study and a case-control study confirmed an association between GA and diabetes, hyperlipidemia, hypothyroidism, and rheumatoid arthritis.^{3,4} Among these, diabetes and hyperlipidemia are the most frequently reported. Hypothyroidism and rheumatoid arthritis were also found to be associated with GA but occurred less frequently.^{3,4} Although there have been reports of GA occurring in patients with malignancies, a definitive relationship remains unproven.³

Although the exact pathogenesis of GA remains unclear, histopathological and molecular studies revealed key immune mechanisms. Both localized and generalized GA share key histologic features, including dermal lymphohistiocytic infiltrates and collagen degeneration.⁵ A delayed-type hypersensitivity reaction appears central, with Th1 lymphocytes stimulating macrophages to release IFN- γ and matrix metalloproteinases (MMPs), resulting in collagen degradation.⁶ Recent studies demonstrate upregulation of Th1 and JAK-STAT signaling pathways, with increased expression of cytokines such as TNF- α , IL-1 β , IFN- γ , IL-12/23p4, oncostatin M, IL-15, and IL-21, underscoring the role of these pathways in GA pathogenesis.⁷

GGA remains a treatment challenge for many clinicians due to the lack of FDA-approved therapies and the unpredictable success rate of many reported therapies.⁷ Unlike localized GA, which often resolves spontaneously within 1–2 years, generalized GA often follows a more chronic course with lower rates of spontaneous resolution. This often necessitates systemic treatment or phototherapy, as therapies effective for localized disease like topical or intralesional corticosteroids, are frequently ineffective for GGA.^{5,7} Systemic treatments include dapsone, antimalarials (hydroxychloroquine, chloroquine), tetracycline antibiotics, isotretinoin, and fumaric acid esters.^{5,8} Phototherapy, such as UVB or PUVA, has shown promising results in case reports.^{9–11}

Given the limited and inconsistent efficacy of conventional therapies, there has been growing interest in immunomodulatory approaches. Recent insights highlighting the role of Th1 activation and JAK-STAT pathway upregulation in GA pathogenesis, support therapeutic rationale for JAK inhibition. Molecular studies demonstrate that JAK blockade normalizes both JAK-STAT-dependent (ie IFN- γ) and JAK-STAT-independent cytokines (ie TNF- α), underscoring JAK-STAT signaling as a key pathogenic driver.¹²

In this systematic review, we will assess the efficacy and safety of different JAK inhibitors in treating GGA.

Materials and Methods

PRISMA Flowchart

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.¹³ The protocol was registered with PROSPERO under the registration number CRD420251029012. A flowchart diagram is presented in [Figure 1](#).

Search Strategy

A comprehensive search was conducted on the following electronic databases: MEDLINE/Pubmed, Web of Science, and Embase. To mitigate publication bias, we implemented a comprehensive, systematic search across multiple databases to reduce the likelihood of missing relevant studies. All databases were searched from inception to April 2025. The specific search strategy used the following terms: “granuloma annulare” OR “generalized granuloma annulare” [Article title/Abstract/Keywords] AND “JAK inhibitor” OR “tofacitinib” OR “ruxolitinib” OR “baricitinib” OR “abrocitinib” OR “Upadacitinib” [Article title/Abstract/Keywords]. Only study types including case reports, case series, observational studies, and clinical trials published in the English-language were considered. Review articles, conference abstracts, preprint papers, books, and book chapters were omitted. To integrate the results from MEDLINE/Pubmed, Web of Science, and Embase, we exported all records into a quality evidence synthesis and management software (Covidence). During this process, duplicate records were removed both automatically by the Covidence software and manually by the reviewers. Titles and abstracts were first screened based on predefined inclusion and exclusion criteria, after which full-text reviews were conducted for the articles that met initial eligibility.

Study Population–Selection

The following PICO (Population, Intervention or exposure, Comparison, Outcome) elements were applied as inclusion criteria for this systematic review: (i) Population: patients diagnosed with GGA of any age or sex, excluding patients with localized GA only, (ii) Intervention: any JAK inhibitor, such as abrocitinib, baricitinib, tofacitinib, upadacitinib, or ruxolitinib (iii) Comparison: This review does not have any comparators, (iv) Outcome: clinical improvement or complete resolution of symptoms, the occurrence of adverse effects, and the timing of treatment response.

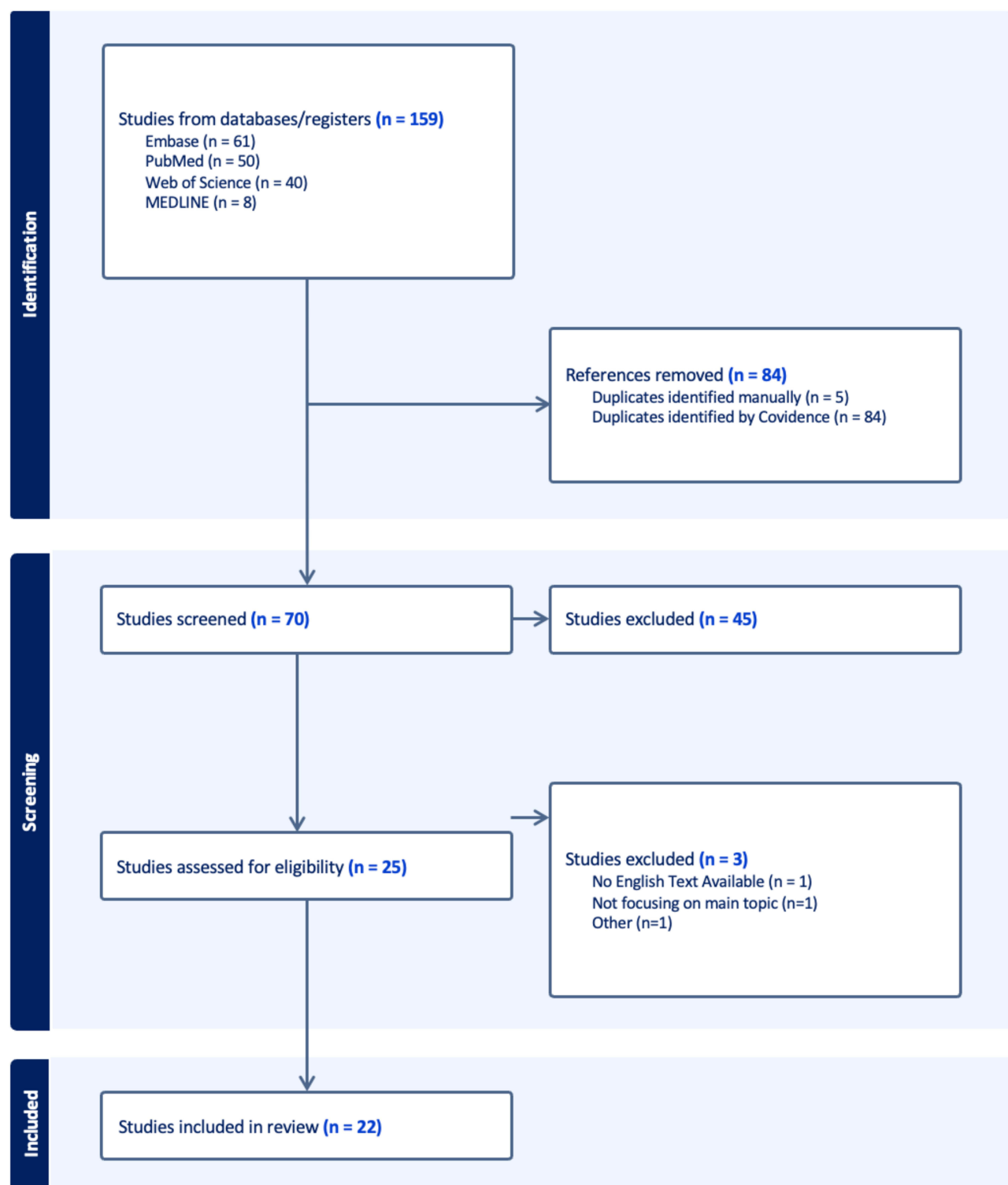


Figure 1 PRISMA 2020 flowchart describing the inclusion methodology applied in review process.

Data Extraction

For all studies that met the inclusion criteria, two independent reviewers (D.J. and S.J.) extracted data using a standardized, predefined form. Any discrepancies were resolved by a third reviewer (B.G). The following information was collected for each study: first author, year of publication, study type, number of patients, patient demographics (age,

sex), medical comorbidities, prior treatments, JAK inhibitor used, dosage, route of administration, time to initial response, clinical outcome, achievement of complete clearance, reported adverse effects, and presence of relapse (Table 1). Risk of bias was assessed using appropriate tools based on study type: the JBI Critical Appraisal Tool for Case Series, the JBI Critical Appraisal Tool for Case Reports, and the ROBINS-I tool for the clinical trial. Full appraisal results are presented in the [appendix \(Tables A1–A3\)](#).

Results

The initial search using the predefined criteria identified 159 publications. After removing 89 duplicates, 70 studies remained for screening. Of these, 22 met inclusion criteria and were included in this review (Figure 1). Most studies had a high risk of bias due to their design (case reports or case series), lack of randomization, and limited blinding. Only one included study was a randomized controlled trial, which was assessed as having a moderate risk of bias due to potential issues in outcome measurement. This trial relied on clinical assessments of BSA involvement, histology, and cytokine levels, with unblinded outcome assessors, raising concerns about measurement bias, particularly for subjective outcomes like BSA and quality of life (Skindex-16). Full risk-of-bias assessments are available in the appendix (Tables A1–A3). Figure 2 demonstrates the total number of patients treated with each JAK Inhibitor and Figure 3 illustrates the overall response to each JAK inhibitor across included studies. Across all included studies, the median time to initial clinical response was 5 weeks (IQR 2.75–8 weeks) and for patients with complete response, time to clearance was 17.6 weeks (IQR 15.5–19.2 weeks). Table 1 summarizes detailed information on dosing regimens, time to response, time to clearance, and relapse following treatment discontinuation for individual studies.

Abrocitinib

One case report evaluated the efficacy of abrocitinib in a 77-year-old female with GGA who had previously failed prior therapy with a topical steroid and bath PUVA. The patient experienced fading of lesions after 2 weeks, with complete resolution by 3 months. Treatment began with 200 mg/day for 1 week, followed by 100 mg/day for 3 months, then tapered to 100 mg every other day for 2 months. No relapse was observed 6 months after treatment cessation.¹⁴

Baricitinib

A total of 11 patients across 4 case reports and 3 case series were treated with baricitinib for GGA, with doses ranging from 2–4 mg/day. All patients had failed at least one prior therapy. Time to initial clinical response ranged from 2 to 14 weeks, with a median of 6 weeks (IQR 4.5–7.5 weeks). Most patients demonstrated significant improvement, with 3 patients achieving complete response. Relapse was noted in 2 patients following treatment discontinuation. One patient relapsed just 3 days after stopping baricitinib, another after 1 month. Adverse effects were generally minimal, though one patient experienced systemic symptoms including fever, sore throat, gastrointestinal upset, and insomnia. Herpes zoster was reported in another case, leading to temporary treatment interruption.^{15–21}

Tofacitinib

A total of 27 patients across 1 case report, 1 clinical trial, and 4 case series were treated with tofacitinib for GGA. All patients had previously failed one or more therapies. Of these patients, 26 were given 5 mg oral tofacitinib twice daily and one patient was given topical 2% ointment twice daily. Time to initial response occurred between 1 week and 3 months, all patients showing significant clinical improvement and 18 showing complete clearance. For patients with complete response, median time to clearance was 17.6 weeks (IQR 17.6–24 weeks). Relapse was reported in two patients following discontinuation of tofacitinib after 1 and 3 months. In both cases lesions resolved after re-initiation of treatment. Adverse events were uncommon. Two patients developed hyperlipidemia, and one patient experienced two uncomplicated urinary tract infections.^{12,22–26}

Upadacitinib

A total of 10 patients across 6 case reports and 1 case series were treated with Upadacitinib for GGA. All patients had recalcitrant disease and had failed multiple previous therapies. Patients were prescribed oral upadacitinib with dosages

Table 1 Characteristics of Included Studies Evaluating JAK Inhibitors for Generalized Granuloma Annulare

Author (Year)	Study Type	Sample size	Age	Sex	Other Medical Conditions	Previous Treatments	Posology	Time to Initial Response	Result & Time to Clearance (if Available)	Relapse?	Adverse Effects
Abrocitinib											
Michels A (2024) ¹⁴	Case Report	1	77	Pt 1: F	NR	Top. steroids, bath PUVA	200mg QD for 1 week, 100mg QD for 3 months, 100mg QAD for 2 months	Pt 1: 2 weeks	Pt 1: CR at 3 months	None at 6 months follow up	Pt 1: Nausea and herpes labialis at week 1
Baricitinib											
Yunoki (2025) ¹⁵	Case Series	2	Pt 1: 51 Pt 2: 62	Pt 1: M Pt 2: F	Pt 1: HTN Pt 2: DLP	Pt 1: Tranilast, NBUVB Pt 2: High potency top. corticosteroid, Tranilast	All pts: 2 mg QD	NR	Pt 1: PR (Markedly flattened at 9 weeks) Pt 2: PR (Marked improvement at 12 weeks)	Pt 1: None at time of publication Pt 2: NR	NR
Kim D (2023) ¹⁶	Case Series	2	Pt 1: 67 Pt 2: 40	All F	Pt 1: DM and HTN Pt 2: NR	Pt 1: Methotrexate, cyclosporine, NBUVB, top. tacrolimus Pt 2: Immunosuppressants (unspecified), top. tacrolimus	Pt 1: 4mg QD for 6 weeks, then 2 mg QD Pt 2: 4mg QD	NR	Pt 1: PR (Dramatic clearing at 6 weeks) Pt 2: Near CR at 4 weeks	Pt 1: 3 days after voluntary discontinuation Pt 2: None at 8 week follow up	NR
Ballová A (2022) ¹⁷	Case Report	1	57	Pt 1: F	Pt 1: RA	Pt 1: Top. betamethasone dipropionate	Unspecified	Pt 1: 2 weeks	Pt 1: CR	NR	NR
Jadoul A (2023) ¹⁸	Case Report	1	66	Pt 1: F	Pt 1: Obesity, HTN, multinodular goiter, hemochromatosis	Pt 1: Top. corticosteroids, UVB therapy, cryotherapy, cyclosporine, adalimumab	Pt 1: 4mg QD, paused due to adverse effect, then tapered to 2mg QD	Pt 1: 6 weeks	Pt 1: PR (Rapid improvement)	None at 8 months follow up	Pt 1: Herpes zoster
Yan TM (2022) ¹⁹	Case Report	1	67	Pt 1: M	NR	Pt 1: Hydroxychloroquine, fluticasone propionate cream, halometasone cream, NBUVB	Pt 1: 4mg QD	Pt 1: 12 weeks	Pt 1: Near CR at 5 months	NR	NR
Khurana (2025) ²⁰	Case Series	3	Pt 1: 48 Pt 2: 60 Pt 3: 59	All F	Pt 1: DM, DLP, rheumatoid nodules. Pt 2: DM Pt 3: NR	Pt 1: Hydroxychloroquine, top. corticosteroids. Pt 2: Top. corticosteroids, dapsone. Pt 3: PO steroids	All pts: 4mg QD	Pt 1: 6 weeks Pt 2: 8 weeks Pt 3: 4 weeks	Pt 1: CR of hand lesions & PR of foot lesions at 14 weeks Pt 2: PR at 12 weeks Pt 3: CR at 6 weeks	Pt 1: 1 month after stopping therapy Pt 2: NR, baricitinib discontinued due to insufficient efficacy. Pt 3: None at 5 month follow up	Pt 1: fever, sore throat, GI disturbance, and insomnia Pt 2: NR Pt 3: NR
Kim A (2024) ²¹	Case Report	1	75	Pt 1: M	Pt 1: HTN, T2D	Pt 1: PO minocycline, top. steroids, triamcinolone, IL injection, cryotherapy	Pt 1: 4mg QD + top. steroid	NR	Pt 1: CR at 14 weeks	None at 24 week follow up	NR
Tofacitinib											
Damsky W (2020) ¹²	Case Series	1	66	Pt 1: F	NR	Pt 1: Hydroxychloroquine, NBUVB, doxycycline, prednisone, cyclosporine, isotretinoin	Pt 1: 5mg BID	Pt 1: 8 weeks	Pt 1: CR at 7 months	NR	NR
Durgin J (2020) ²²	Case Report	1	46	Pt 1: F	Pt 1: None	Pt 1: Hydroxychloroquine, top. tacrolimus, dapsone	Pt 1: 2% ointment BID	NR	Pt 1: Almost CR at 12 weeks	None 2 months following treatment	NR

(Continued)

Table I (Continued).

Author (Year)	Study Type	Sample size	Age	Sex	Other Medical Conditions	Previous Treatments	Posology	Time to Initial Response	Result & Time to Clearance (if Available)	Relapse?	Adverse Effects
McPhie M (2021) ²³	Case Series	2	Pt. 1: 78 Pt. 2: 59	Pt. 1: F Pt. 2: F	Pt 1: RA, osteoarthritis, Meniere's disease Pt 2: HTN	Pt. 1: Corticosteroids (top. and IL), phototherapy, methotrexate, ustekinumab Pt. 2: Top. and IL corticosteroids, top. calcineurin inhibitors, phototherapy, ustekinumab	All pts: 5mg BID	Pt 1: 4 weeks Pt 2: 1 week	Pt 1: Almost CR at 9 months Pt 2: PR (thinning of plaques with no new lesions) at 4 weeks	NR	NR
Wang A (2021) ²⁴	Clinical Trial	5	62±5.2	NR	NR	Pts 1–5: Corticosteroids (PO and injectable), hydroxychloroquine, cyclosporine, pentoxifylline, PO antibiotics, phototherapy	All pts: 5mg BID	Pts 1–5: 1–3 months	Pt 1: PR at 6 months Pt 2: CR at 6 months Pt 3: PR at 6 months Pt 4: CR at 6 months Pt 5: CR at 6 months	NR	1 pt with two uncomplicated UTIs
Bosch-Amate (2022) ²⁵	Case Series	3	Pt 1: 69 Pt 2: 73 Pt 3: 64	Pt 1: F, Pt 2: F, Pt 3: M	Pt. 1: NR Pt. 2: DLP Pt. 3: NR	Pt 1: PO corticosteroids, retinoic and tranexamic acid, indomethacin, hydroxychloroquine, methotrexate Pt. 2: PO corticosteroids, hydroxychloroquine, pentoxifylline, dapsone Pt. 3: PO corticosteroids, phototherapy, methotrexate, hydroxychloroquine, adalimumab	All pts: 5mg BID	NR	Pt 1: CR at 4 months Pt 2: CR at 8 months Pt 3: CR at 6 months	NR	NR
Dev A (2025) ²⁶	Retrospective Case Series	15	53.9 ± 9.1	13 F, 2 M	7 pts with DM, 4 with HTN, anemia and HT in 2 each, and DLP and depressive disorder in one each	9 received prior treatment including top. steroids, top. tacrolimus, oral steroids, acitretin, isotretinoin, dapsone, doxycycline, hydroxychloroquine	All pts: 5mg BID	NR	11 pts with CR (4.4 ± 2.1 months) 4 pts with PR (7.3 ± 2.8 months)	2 patients with recurrence at 1 month and 3 months respectively after stopping tofacitinib. Resolved promptly after re-administering tofacitinib for 1 month	Hyperlipidemia in 2 pts
Upadacitinib											
Chen Y (2024) ²⁷	Case Report	1	Pt 1: 53	M	Pt 1: DLP	Pt 1: Top. and PO corticosteroids, methotrexate, NBUVB	Pt 1: 15mg QD for 4 weeks; then 15 mg QAD for 4 weeks; then 15 mg every 2 days for 4 weeks	Pt 1: 2 weeks	Pt 1: CR at 8 weeks	None at 6 months	NR
De Greef A (2024) ²⁸	Case Report	1	Pt 1: 50s	F	Pt 1: Livedoid vasculopathy	Pt 1: Top. corticosteroids, hydroxychloroquine (200–400mg/day), doxycycline 200mg/day, methotrexate 12.5mg/week and vitamin E	Pt 1: 30mg QD	Pt 1: 8 weeks	Pt 1: CR at 6 months	None at two-month follow-up after treatment cessation	Pt 1: Hyperlipidemia

Coican A (2024) ²⁹	Case Report	2	Pt 1: 60 Pt 2: 21	F	Pt 1: HT and DM Pt 2: NR	Pt 1: Rifampin, ofloxacin, minocycline, ultrapotent top. steroids, dapsone, hydroxychloroquine, narrowband UVB, pentoxifylline, adalimumab. Pt 2: Top. steroids, PO steroids, methotrexate, hydroxychloroquine, low-dose naltrexone, apremilast	All pts: 15mg BID	Pt 1: 8 weeks Pt 2: 3 weeks	Pt 1: CR at 4 months Pt 2: CR at 2 months	Pt 1: None at 6mo follow up Pt 2: NR	Pt 1: NR Pt 2: mild headaches
Sondermann W (2021) ³⁰	Case Report	1	Pt 1: 61	F	Pt 1: DM, obesity, CHD and RA	Pt 1: Mometasone furoate ointment, clobetasol propionate ointment, and etanercept	Pt 1: 15mg QD	Pt 1: 6 weeks	Pt 1: Almost CR by 4 months.		NR
Slater K (2023) ³¹	Case Report	1	Pt 1: 57	F	Pt 1: DM, HT, kidney disease	Pt 1: Clomitrazone 1% cream, triamcinolone 1% cream, NBUVB, clobetasol 0.05% cream, rifampin 600mg, ofloxacin 400mg, minocycline 100mg, IL triamcinolone, ruxolitinib 2% cream	Pt 1: 15mg QD	Pt 1: 4 weeks	Pt 1: CR	None at time of publication, pt remained on maintenance therapy with 15 mg QD	NR
Trees, A (2024) ³²	Case Report	1	Pt 1: 61	F	Pt 1: HT	Pt 1: Triamcinolone 0.1% cream, clobetasol 0.05% cream, PO prednisone	Pt 1: 15mg TIW for 2 months, then 15mg BIW	NR	Pt 1: CR at 4 weeks	None at time of publication while continuing to taper treatment	NR
Zheng J (2024) ³³	Case Series	3	Pt 1: 52 Pt 2: 60 Pt 3: 61	All F	NR	Pt 1: cortisone cream, clobetasol propionate 0.05% cream, tacrolimus 0.1% cream, NBUVB Pt 2: dapsone 100mg Pt 3: clobetasol propionate 0.05% cream, methotrexate, NBUVB	All pts: 30mg QD later reduced to 15mg QAD due to adverse effects	NR	Pt 1: PR (improvement in erythema and prominence) at 12 weeks Pt 2: PR (Significant improvement marked by reduced border elevation) at 2 weeks Pt 3: PR (Significant improvement with reduction in size and intensity of lesions) at 8 weeks	None at the time of publication	Pt 1: generalized weakness at 30mg daily Pt 2: lesion in oral cavity, strep throat, COVID-19, bone pains, and abdominal cramps at 30mg daily Pt 3: Acne at 30mg daily
Ruxolitinib											
Piontkowski AJ (2024) ³⁴	Case Report	1	51	F	NR	Pt 1: Betamethasone dipropionate 0.05% cream, tacrolimus 0.1% ointment, IL triamcinolone, hydroxychloroquine 200mg	Pt 1: 1.5% cream BID	NR	Pt 1: CR at 12 weeks	None; Ruxolitinib 2–3 times per week for minor flares	NR

Abbreviations: Pt, patient; NR, Not reported; DM, diabetes mellitus; HTN, hypertension; DLP, dyslipidemia; HT, hypothyroidism; BID, twice a day; QD, every day; QAD, every other day; TIW, three times a week; PO, oral; top, topical; intraslesional, IL; NBUVB, narrow band ultraviolet B phototherapy; BSA, body surface area; F, female; M, male; CR, complete resolution; PR, partial resolution.

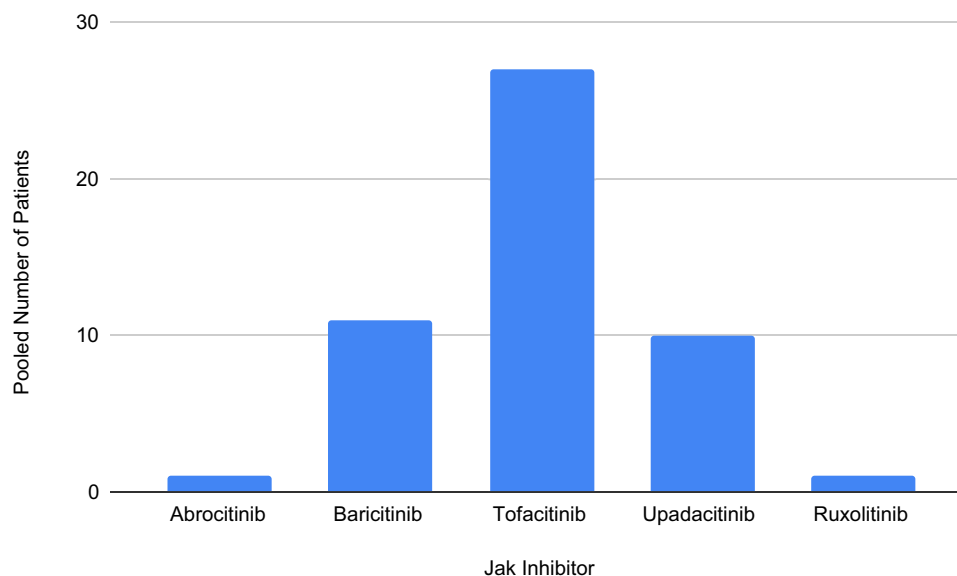


Figure 2 Pooled Number of Patients Treated with Each JAK Inhibitor.

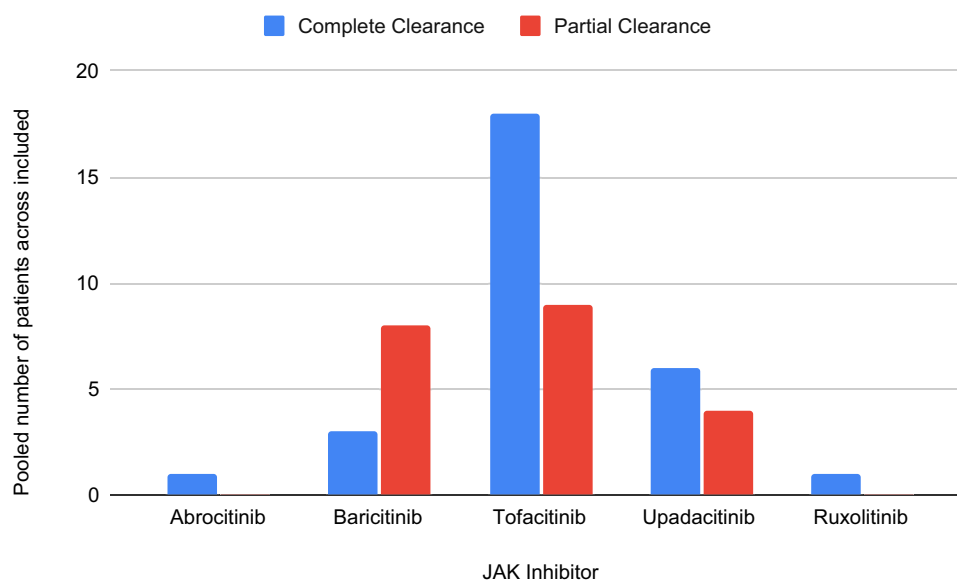


Figure 3 Pooled Treatment Response to JAK Inhibitors in Generalized Granuloma Annulare: Complete vs Partial Clearance.

ranging from 15 mg twice a week to 30 mg twice daily. Time to initial response occurred between 3 and 8 weeks for these patients, with a median of 5 weeks (IQR 3.25–7.5 weeks). In patients with complete response, median time to clearance was 8 weeks (IQR 8–16 weeks). 60% of patients (6/10) achieved complete response, and the remaining 40% (4/10) showed near complete response. No relapses were reported. Adverse effects were generally mild and included weakness, oral lesions, infections, bone pain, abdominal cramps, acne, hyperlipidemia, and mild headaches. Most patients did not experience any adverse effects.^{27–33}

Ruxolitinib

One case report described a healthy 51-year-old female who was treated with topical ruxolitinib 1.5% cream twice daily for GGA that was recalcitrant to previous therapies. The patient achieved complete resolution after 12 weeks of twice-

daily application. She remained mostly clear beyond 12 weeks, requiring topical therapy with ruxolitinib two to three times per week to manage minor flares.³⁴

Discussion

Granuloma annulare, particularly its generalized form (GGA), continues to present a significant therapeutic challenge due to its often refractory nature and the absence of FDA-approved treatments. Our systematic review, encompassing 22 studies, highlights the emerging role of JAK inhibitors as a promising targeted therapy for GGA.

Our findings indicate that JAK inhibitors consistently demonstrate clinical improvement in patients with GGA, often leading to complete or near-complete lesion clearance. Complete response was reported in 58.0% (29/50) and partial or near complete response in 42.0% (21/50) of patients. Tofacitinib, with 27 patients across various study types, showed significant clinical improvement in all cases, with (18/27) 66.7% achieving complete clearance. Similarly, baricitinib treatment resulted in significant improvement for most patients across 11 cases, while upadacitinib led to improvement in all 10 reported cases, with (6/10) 60% achieving complete clearance. One patient on Abrocitinib had complete response. Even topical ruxolitinib showed complete resolution in one reported case. These results are particularly encouraging given that most included patients had a history of refractory disease, having failed numerous conventional systemic and topical therapies. The median time to initial response was 5 weeks (IQR 2.75–8 weeks) suggesting a relatively rapid therapeutic effect compared to some traditional treatments. For patients with complete response, median time to clearance was 17.6 weeks (IQR 15.5–19.2 weeks).

The safety profile of JAK inhibitors in this GGA cohort appears acceptable, with most reported adverse effects being mild and consistent with the known side effects of these agents in other dermatologic conditions. Importantly, no new safety signals were identified. Reported side effects mirrored those of larger trials of JAK inhibitors, primarily hyperlipidemia and infections (eg herpes labialis, urinary tract infections, respiratory infections, and herpes zoster).³⁵ Relapse was observed in a subset of patients upon discontinuation or tapering of the JAK inhibitor, underscoring the potential need for long-term or maintenance therapy, similar to other chronic inflammatory conditions.

Molecular studies previously indicated that JAK blockade not only normalizes JAK-STAT pathway associated cytokines like IFN- γ but also non-JAK-STAT-dependent cytokines such as TNF- α , suggesting a pivotal role for JAK-STAT pathway upregulation as a key driver in GA pathogenesis.¹² The clinical efficacy demonstrated by JAK inhibitors in this review provides further evidence supporting this hypothesized mechanism. By targeting this inflammatory pathway, JAK inhibitors offer a more targeted approach, potentially leading to a more predictable efficacy for patients with GGA.

This review is limited by the quality of the available evidence, as included studies were primarily case reports and case series. Additionally, heterogeneity among the included studies, including differences in study design, dosing regimens, treatment duration, and outcome definitions limits the interpretability of pooled findings. Most case reports lacked detailed information on patient follow-up and specific outcome measurements, while case series often did not include control groups. This limits our ability to draw definitive conclusions regarding efficacy and safety. Only one included study was a randomized controlled trial, which, despite its higher methodological rigor, was assessed as having a moderate risk of bias due to potential issues in outcome measurement. This absence of larger, well-controlled clinical trials limits the generalizability of our findings. Lastly, our review was limited to English-language literature, which might introduce language bias.

Conclusions

JAK inhibitors show promise as a targeted therapy for GGA, offering a novel and often effective approach for patients with refractory disease who have exhausted traditional treatment options. Their ability to induce clinical improvement and complete clearance in a notable proportion of patients, coupled with a manageable safety profile, makes them a valuable addition to the limited therapeutic options for GGA. JAK inhibitors may be considered for patients with refractory GGA who have not responded to standard therapies, with careful shared decision making regarding their off-

label use. However, further high-quality, randomized controlled trials are needed to establish long-term efficacy, safety, optimal dosing regimens, and long-term safety outcomes for JAK inhibitors in the management of GGA.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Statement

EC approval was not required since human subjects were not directly involved in the present study.

Consent for Publication

Consent for publication was not required as this manuscript does not include any individual data, images, videos, or other identifiable materials.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

Dr. Alison Ehrlich has previously served as an investigator in clinical trials involving baricitinib and upadacitinib. All other authors declare no conflicts of interest.

References

1. Thornsberry LA, English JC. 3rd. Etiology, diagnosis, and therapeutic management of granuloma annulare: an update. *Am J Clin Dermatol*. 2013;14(4):279–290. doi:10.1007/s40257-013-0029-5
2. Piette EW, Rosenbach M. Granuloma annulare: clinical and histologic variants, epidemiology, and genetics. *J Am Acad Dermatol*. 2016;75(3):457–465. doi:10.1016/j.jaad.2015.03.054
3. Barbieri JS, Rosenbach M, Rodriguez O, Margolis DJ. Association of granuloma annulare with type 2 diabetes, hyperlipidemia, autoimmune disorders, and hematologic malignant neoplasms. *JAMA Dermatology*. 2021;157(7):817–823. doi:10.1001/jamadermatol.2021.1805
4. Leasure AC, Damsky W, Cohen JM. Comorbidities associated with granuloma annulare: a case-control study in the all of us research program. *J Am Acad Dermatol*. 2022;87(1):197–199. doi:10.1016/j.jaad.2021.07.033
5. Lukacs J, Schliemann S, Elsner P. Treatment of generalized granuloma annulare – a systematic review. *J Eur Acad Dermatol Venereol*. 2015;29(8):1467–1480. doi:10.1111/jdv.12976
6. Schmieder SJ, Harper CD, Schmieder GJ. Granuloma Annulare. *StatPearls*. 2025.
7. Wang J, Khachemoune A. Granuloma annulare: a focused review of therapeutic options. *Am J Clin Dermatol*. 2018;19(3):333–344. doi:10.1007/s40257-017-0334-5
8. Keimig EL. Granuloma Annulare. *Dermatol Clin*. 2015;33(3):315–329. doi:10.1016/j.det.2015.03.001
9. Hindson TC, Spiro JG, Cochrane H. PUVA therapy of diffuse granuloma annulare. *Clin Exp Dermatol*. 1988;13(1):26–27. doi:10.1111/j.1365-2230.1988.tb00644.x
10. Kerker BJ. Photochemotherapy of generalized granuloma annulare. *Arch Dermatol*. 1990;126(3):359–361. doi:10.1001/archderm.1990.01670270091015
11. Schnopp C, Tzaneva S, Mempel M, Schulmeister K, Abeck D, Tanew A. UVA1 phototherapy for disseminated granuloma annulare. *Photodermatol Photoimmunol Photomed*. 2005;21(2):68–71. doi:10.1111/j.1600-0781.2005.00145.x
12. Damsky W, Thakral D, McGeary MK, Leventhal J, Galan A, King B. Janus kinase inhibition induces disease remission in cutaneous sarcoidosis and granuloma annulare. *J Am Acad Dermatol*. 2020;82(3):612–621. doi:10.1016/j.jaad.2019.05.098
13. Page MJ, McKenzie JE, Bossuyt PM, et al. Declaración PRISMA 2020: una guía actualizada para la publicación de revisiones sistemáticas. *Rev Esp Cardiol*. 2021;74(9):790–799. doi:10.1016/j.recsep.2021.06.016
14. Michels A, Heiland R, Hammerschmidt S, et al. Successful treatment of recalcitrant generalized granuloma annulare with the JAK inhibitor abrocitinib. *J Dtsch Dermatol Ges*. 2024;22(6):841–843. doi:10.1111/ddg.15426
15. Yunoki M, Kondo S, Otsuka M, Tokura Y. Case report: generalized granuloma annulare successfully treated with baricitinib in two cases. *J Cutaneous Immunol Allergy*. 2025;7:13892. doi:10.3389/jcia.2024.13892

16. Kim D, Kang HY. Rapid improvement of refractory generalized granuloma annulare with the Janus kinase inhibitor baricitinib in two patients. *Clin Exp Dermatol*. 2023;48(4):375–376. doi:10.1093/ced/llac110
17. Ballova A, Kmecova Z, Pec J, Voreckova K. Recalcitrant granuloma annulare induced by two different biologic agents resolved after Janus kinase inhibitor treatment. *Dermatol Ther*. 2022;35(8):e15641. doi:10.1111/dth.15641
18. Jadoul A, Huygen L, Leemans G, Grosber M, Kortekaas Krohn I, Gutermuth J. JAK1/2 pathway-specific treatment of disseminated granuloma annulare with baricitinib. *J Eur Acad Dermatol Venereol*. 2023;37. doi:10.1111/jdv.19073
19. Yan TM, Zhang H, Wu XY, Zhang ZY. Successful treatment of generalized granuloma annulare with baricitinib. *J Eur Acad Dermatol Venereol*. 2022;36(7):e500–e502. doi:10.1111/jdv.18031
20. Khurana A, Sharath S, Bansal A, Sardana K, Kathirvelu AP, Muddebihal A. Variable therapeutic outcomes with baricitinib in refractory generalised granuloma annulare - Need for type specific cytokine data. *Indian J Dermatol Venereol Leprol*. 2025;1–3. doi:10.25259/IJDVL_1511_2024
21. Ki A, Kang HJ, Lim Y. Generalized granuloma annulare treated with baricitinib in elderly patient. *Korean J Dermatol*. 2024;62(10):571–573.
22. Durgin JS, Shields BE, Rosenbach M. Generalized granuloma annulare: a widespread response to limited application of compounded 2% topical tofacitinib. *JAAD Case Rep*. 2020;6(10):1113–1115. doi:10.1016/j.jdc.2020.07.054
23. McPhie ML, Swales WC, Gooderham MJ. Improvement of granulomatous skin conditions with tofacitinib in three patients: a case report. *SAGE Open Med Case Rep*. 2021;9:2050313X211039477. doi:10.1177/2050313X211039477
24. Wang A, Rahman N-T, McGearry MK, et al. Treatment of granuloma annulare and suppression of proinflammatory cytokine activity with tofacitinib. *J Allergy Clin Immunol*. 2021;147(5):1795–1809. doi:10.1016/j.jaci.2020.10.012
25. Bosch-Amate X, Serra-García L, Alamon-Reig F, et al. Treatment of granuloma annulare with tofacitinib. *Australas J Dermatol*. 2022;63(3):400–403. doi:10.1111/ajd.13875
26. Dev A, Keshavamurthy V, Chatterjee D. Therapeutic success of tofacitinib in granuloma annulare: a retrospective case series of 15 patients. *Indian J Dermatol Venereol Leprol*. 2024;91(1):65–70. doi:10.25259/IJDVL_215_2024
27. Chen Y, Mao J, Bao S, Zhuang Z, Gong T, Ji C. Effective treatment of recalcitrant generalized papular granuloma annulare with upadacitinib monotherapy: a case report and literature review. *Skin Res Technol*. 2024;30(10):e70092. doi:10.1111/srt.70092
28. De Greef A, Benjelloun G, Harkemanne E, Baecq M. Successful treatment of disseminated granuloma annulare with upadacitinib. *Dermatol Ther*. 2024;14(3):813–817. doi:10.1007/s13555-024-01117-z
29. Coican A, Meckley A, Sagasser N, Greenfield M, Song EJ, El-Bahri J. Successful treatment of refractory generalized granuloma annulare with upadacitinib. *Case Reports Dermatolog Med*. 2024;2024:8859178. doi:10.1155/2024/8859178
30. Sondermann W, Hadaschik E, Specker C. Successful therapy of disseminated patch-type granuloma annulare with upadacitinib in a patient with rheumatoid arthritis. *Dermatol Ther*. 2022;35(1):e15211. doi:10.1111/dth.15211
31. Slater KN, Valk B, Kartono F. A case of generalized granuloma annulare treated with upadacitinib. *JAAD Case Rep*. 2023;34:12–14. doi:10.1016/j.jdc.2023.01.027
32. Trees A, Smithem C, Bialick M, Kabigting F. Treatment of disseminated granuloma annulare with pulse therapy upadacitinib. *Dermatol Online J*. 2024;30(5). doi:10.5070/D330564430
33. Zheng J, Sharma S, Wassell K, Lanzini R, Lima H. Letter to the Editor: effective treatment of disseminated granuloma annulare with upadacitinib. *JAAD Case Rep*. 2024;44:98–100. doi:10.1016/j.jdc.2023.11.024
34. Piontkowski AJ, Wei N, Mumtaz A, Gulati N. Ruxolitinib cream for the treatment of granuloma annulare. *JAAD Case Rep*. 2024;50:62–64. doi:10.1016/j.jdc.2024.05.030
35. Kraev K, Geneva-Popova MG, Hristov BK, et al. Examining the safety profile of Janus Kinase (JAK) inhibitors in the management of immune-mediated diseases: a comprehensive review. *Life*. 2023;13(12). doi:10.3390/life13122244

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