Pediatric Dermatology

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REVIEW ARTICLE OPEN ACCESS

Blau Syndrome (Juvenile Systemic Granulomatosis): State-Of-The-Art Review

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Received: 15 January 2025 | **Revised:** 26 April 2025 | **Accepted:** 23 May 2025

Funding: The authors received no specific funding for this work.

Keywords: arthritis | Blau syndrome | granulomatous diseases | NOD2 | sarcoidosis | uveitis

ABSTRACT

Blau syndrome (BlauS) is a rare pediatric autoinflammatory disorder due to *NOD2* gain-of-function pathogenic variants characterized by a triad of granulomatous dermatitis, arthritis, and uveitis, which can progress to systemic complications if untreated. Skin and joint findings typically emerge by age 2 years, with ocular involvement appearing around age 4 years. Early biologic intervention, particularly with anti-TNF-α therapies, can prevent severe complications like joint destruction and blindness. Systemic corticosteroids serve as bridging therapy, while methotrexate and thalidomide may help but are often insufficient as monotherapy. IL-1 and IL-6 inhibitors, as well as tofacitinib, are options for refractory cases.

1 | Introduction

Blau syndrome (BlauS), a rare pediatric autoinflammatory disorder, is caused by pathogenic variants in the *NOD2/CARD15* gene and manifests with granulomatous inflammation affecting multiple organs. This disorder presents with hallmark symptoms—granulomatous dermatitis, arthritis, and uveitis—and can result in significant morbidity if not diagnosed and managed early. There are currently no guidelines on the diagnosis and management of BlauS [1]. Due to the rarity of reported cases, a comprehensive review is helpful in synthesizing the existing body of literature on BlauS, including recent advances in diagnosis and management. This review examines the epidemiology, pathophysiology, clinical findings, and proposed treatment algorithms.

BlauS is caused by a heterozygous pathogenic variant in the *CARD15/NOD2* gene, located on chromosome 16q12. While BlauS is typically associated with a single pathogenic variant per patient, a case series of 50 patients found over 15 different *NOD2* pathogenic variants [2], with the most pathogenic variants affecting the *p.R334W* locus. The NOD2 protein acts as a pattern recognition receptor for bacterial peptidoglycans and functions to activate NF-κB downstream during inflammation. Gain-of-function pathogenic variants lead to excessive activation of pro-inflammatory cytokines, which in turn promote the formation of granulomas in various tissues, disrupting immune homeostasis. These pathogenic variants are involved in other autoinflammatory conditions such as Crohn's disease. The abnormal activation of inflammatory pathways through *NOD2* may contribute to the pathogenesis of diabetes, cardiovascular, and cerebrovascular disease, linking immune dysregulation to systemic complications [3]. While this has been supported by mechanistic and animal studies, clinical evidence remains limited, necessitating further investigation.

The first eleven cases of BlauS spanned four generations and were identified by Edward Blau in 1985 [4], who recognized autosomal dominant inheritance. In 2001, point mutations were found in the *NOD2* gene in patients with BlauS [5]. Before genetic

testing was available, sporadic cases of BlauS were reported in the literature as early-onset sarcoidosis (EOS). Now, both can be classified under the unifying term, "juvenile systemic granulomatosis" [6]. Due to the rarity of BlauS, no high-quality, large-scale randomized controlled trials have been done, resulting in limited guidance on therapeutic strategies, particularly biologic agents like anti-TNF-α therapies and tofacitinib. Gaps in the literature include the lack of consensus on clinical diagnostic criteria, distinguishing presentations and management of pediatric- and adult-onset BlauS, and knowledge of long-term treatment outcomes.

2 | Epidemiology

BlauS is an exceedingly rare autoinflammatory disorder, with an estimated prevalence of 0.05 per 100,000 person-years [6], equivalent to an incidence of 1 case of BlauS per 2 million people annually. Due to its rarity, the precise epidemiological profile is unclear. The condition is likely underreported, particularly in regions where access to genetic testing and specialized care is limited.

3 | Pathophysiology

At the molecular level, gain-of-function pathogenic variants in *NOD2* result in persistent stimulation of T-helper cells, perpetuating a pro-inflammatory loop. This excessive activation of *NOD2* signaling promotes the overproduction of pro-inflammatory cytokines, with increases in IL-1β, TNF-α, and IL-6 levels [7]. These cytokines, mediated by the dysregulation of *NOD2* signaling and the activation of NF-κB drive the formation and maintenance of granulomas [8], leading to ongoing tissue inflammation and damage in the skin, joints, and eyes. Over time, this chronic inflammation leads to the characteristic clinical features of BlauS-like granulomatous dermatitis, arthritis, and uveitis. These pathways of activation emerge as points of intervention for therapeutic targets, including biologic agents targeted to modulate cytokine production.

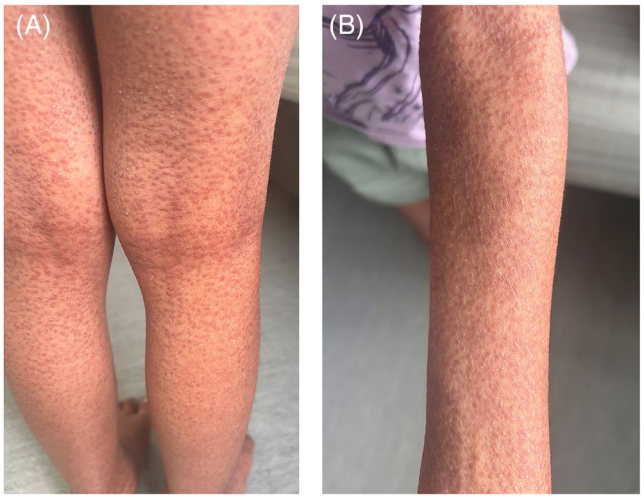

FIGURE 1 | (A, B) Numerous skin-colored and erythematous to brown monomorphic 2–3 mm papules located on the torso, and upper and lower limbs.

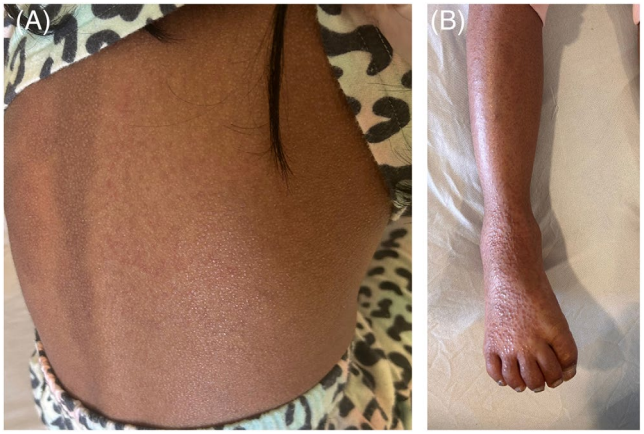

FIGURE 2 | (A) Hyperpigmented monomorphic flat-topped papules on the upper and lower back of a child with Blau syndrome. (B) Hyperpigmented monomorphic flat-topped papules on the right leg and foot of a child with Blau syndrome.

4 | Clinical Manifestations

Clinical manifestations typically start in children under 5 years of age, with the classic triad of dermatitis, arthritis, and uveitis. Cutaneous findings are the first sign and appear as an asymptomatic papular eruption, followed by joint and ocular manifestations within months to a few years. The initial eruption presents as red-brown monomorphous papules with no epidermal changes (Figures 1 and 2), which may later develop a scaly erythematous appearance and become generalized. Affected areas may have a slightly raised, firm texture due to the underlying granulomas. On histopathology, there are non-caseating granulomas composed of epithelioid histiocytes and sparse T lymphocytes (Figure 3) [9].

In addition to the typical granulomatous dermatitis, patients with BlauS may exhibit other cutaneous findings. Skin nodules are a common finding, and although uncommon, some patients present with erythema nodosum-like lesions [10]. Ichthyosis-like lesions, particularly ichthyosis vulgaris-like changes on the lower legs, are another feature that can also be seen in sarcoidosis [8]. Over time, pigmentary changes may develop, with some patients presenting with hyperpigmented macules or patches that appear tan-colored or 'dirty' [7]. One case reported *Propionibacterium acnes*-associated lichenoid eruptions [11]. In some cases, the granulomatous dermatitis can present in middle adulthood [12]. Granulomatous dermatitis in BlauS may resolve spontaneously over time but can recur in intermittent episodes spanning years, sometimes requiring systemic treatment for control. Residual skin changes, like follicular atrophoderma or poikiloderma, can persist even after the active lesions fade [13].

Joint involvement presents as joint effusion, due to granulomatous synovitis and tenosynovitis. Arthritis is commonly chronic and may lead to joint destruction if untreated. The skin and joint findings manifest early in life and occurred at a median of 2 years of age in an international registry, and it appears that skin findings precede joint findings [14]. A prospective cohort

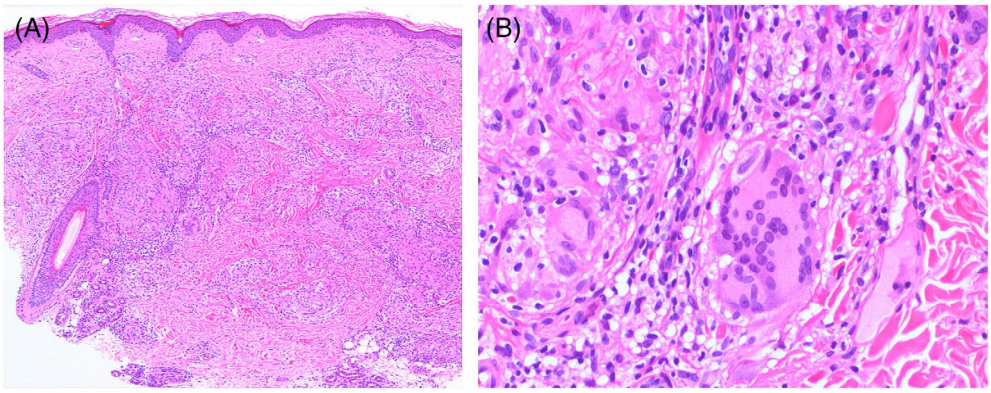

FIGURE 3 | (A) Histopathology showing a multinodular dermal infiltrate of non-caseating, non-palisading granulomas, with sparing of the overlying epidermis (H&E, ×40). (B) Higher power view showing non-caseating granulomas composed of epithelioid histiocytes, some multinucleated, with a surrounding relatively sparse lymphocytic infiltrate (H&E ×200). (Photos courtesy of Dr. Antonio Torrelo.)

study found the median age of onset of the granulomatous rash was 1.1 years, and the onset of joint disease was 2 years [15].

Ocular involvement can be severe in BlauS and delayed treatment leads to significant complications [16]. Acute issues include multifocal choroiditis, papilledema, keratitis, episcleritis, ocular myositis, conjunctivitis, and corneal ulcers. Over time, untreated or poorly managed cases may result in long-term complications of cataracts, glaucoma, posterior synechiae, band keratopathy, cystoid macular edema, retinal detachment, choroidal thickness reduction, corneal perforation, chorioretinal scars, choroidal neovascularization, macular edema, and even optic nerve atrophy [16]. Many patients experience significant visual impairment, and extremely poor visual outcomes or blindness have been reported in more than half of the children. The ocular symptoms generally present later than the cutaneous and joint manifestations, with studies showing a median age of onset at around 4.4 years [14]. The rate of blindness in untreated or inadequately treated patients can be significant, and 14% of inadequately treated patients in a cohort study progressed to blindness. Out of these patients, 71.4% (5 out of 7) were treated with non-biologics exclusively, while 14.3% (1 out of 7) were treated with anti-TNF-α therapy (adalimumab) after delays in diagnosis. After switching from prednisone to adalimumab, the sight in this one patient's affected eye did not deteriorate further [2].

The incidence of cutaneous, joint, and ocular manifestations can vary depending on the specific genetic pathogenic variant. The *p.R334W* pathogenic variant was associated with an earlier onset of skin and joint symptoms, while the *p.R587C* pathogenic variant was associated with a higher incidence of fever [2]. 50% of patients with the *p.R334W* pathogenic variant had skin symptoms by 2.1 years of age, while less than 50% of patients with the *p.R587C* pathogenic variant had skin symptoms until after 15 years of age, suggesting a significantly later average age of onset. For those with the *p.R587C* pathogenic variant, joint and eye symptoms were more frequent, affecting 75% of patients by 15 years. All patients with the *R334W* pathogenic variant had joint symptoms, compared with 70% of those with the *R587C* pathogenic variant. The full triad presented more frequently in patients with the *R334W* pathogenic variant. Despite variations in pathogenic variants, mechanisms driving the risk for ocular involvement and its onset, severity, and progression are not well defined [2]. Proposed therapeutic strategies are categorized based on ocular involvement and focus on prevention when ocular symptoms are absent, given the aggressive nature of the condition. Patterns that predict the development of ocular involvement would allow for earlier intervention and better outcomes.

One key pitfall to diagnosis occurs in patients with a delayed presentation of the classic triad (i.e., dermatitis, arthritis, uveitis) or an atypical order of symptom onset, which can lower clinical suspicion of BlauS. The clinical presentation of BlauS varies widely, with patients lacking the classic triad and others who present with additional manifestations, such as fever, panniculitis, and granulomatous lymphadenopathy [10]. For example, patients presenting with an isolated papular eruption or arthritis may not raise concerns for a systemic autoinflammatory condition. Nonspecific skin lesions and chronic uveitis in isolation create opportunities for misdiagnosis. Knowledge of these variations in clinical presentation can help the practitioner keep BlauS on the differential diagnosis.

Genetic and environmental triggers can also influence the clinical presentation of BlauS. In several case reports, Bacillus Calmette-Guérin (BCG) vaccinations have been identified as a trigger of BlauS. Granuloma development can occur at the site of vaccination, and this may reflect *Mycobacterium bovis* triggering a local inflammatory response [17, 18]. In a study of 50 confirmed cases of BlauS, nine cases presented following BCG vaccination with a skin eruption at the vaccination site [2]. As well, in vitro studies indicated that *Salmonella enterica* serovar Typhimurium can act as a trigger to enhance the expression of TNF-α mRNA, leading to an exacerbated inflammatory response. The hyperactivation contributes to impaired bacterial clearance, as excessive inflammation can disrupt the proper resolution of the immune response with IL-10 and TGF-β.

Systemic manifestations, including lymphadenopathy, hepatomegaly, and splenomegaly, occur in a large subset of patients, indicating broader reticuloendothelial system involvement [2]. Late-stage systemic manifestations of BlauS are seen in around 52% of patients [15]. In one case report, a patient developed unilateral hip arthritis at 1 year of age and bilateral non-granulomatous uveitis at 3 years, treated with systemic steroids

and methotrexate. Fifteen years after presentation, he developed cervical lymphadenopathy and interstitial lung disease, which responded to increased infliximab dosing and prednisone, resulting in remission of symptoms [19]. Another case described a female who first presented with arthritis at 7 years of age, was diagnosed with BlauS 10 years later, and developed renal vasculitis a year after diagnosis [20]. Systemic manifestations, such as granulomatous lymphadenopathy, hepatosplenomegaly, and large vessel vasculitis, may emerge in adolescence, and patients with BlauS need ongoing monitoring.

5 | Diagnosis

An algorithm was proposed to improve the diagnostic accuracy in pediatric patients presenting with uveitis, arthritis, and dermatitis before the age of 5 years [1]. The algorithm (Table 1) begins with a detailed clinical examination and consults from ophthalmology, rheumatology, and immunology to look for common causes of granulomatous inflammation, such as pulmonary involvement indicative of sarcoidosis and infections including TB and atypical mycobacterial infections. The next step involves genetic testing for *NOD2* pathogenic variants, which can confirm the diagnosis of BlauS. Genetic testing for BlauS commonly involves Sanger sequencing to detect gain-of-function pathogenic variants in specific regions of *NOD2/CARD15*. Next-generation sequencing is used if a broader panel of autoinflammatory disorders needs to be considered [21]. Genetic testing focuses on specific pathogenic variants, such as *R334W* and *R334Q* [7].

BlauS can be misdiagnosed as other granulomatous diseases, such as sarcoidosis, juvenile idiopathic arthritis (JIA), or infections like tuberculosis (TB), due to overlapping clinical features (Tables 2 and 3). Among 123 patients diagnosed with JIA, 26 (21.1%) tested positive for a pathogenic *NOD2* gene variant. Zhong et al. conclude that nine clinical features were associated with a higher likelihood of BlauS, including a positive family history, destructive arthritis, cutaneous lesions preceding the arthritis, and negative antinuclear antibody testing. With molecular confirmation of BlauS, 38.5% of diagnosed patients had a change in clinical management, including escalation of treatment with TNF-α inhibitors or conventional synthetic disease-modifying antirheumatic drugs. Given the overlapping features of arthritis, JIA should be considered, and TB must be ruled out due to its granulomatous nature if histopathology is not provided. In the presence of non-caseating granulomas, the principal pathologic differential diagnosis is sarcoidosis, as its histologic findings are identical to those seen in Blau syndrome. Other conditions featuring cutaneous infiltrates of non-caseating, non-palisading granulomas can share overlapping histologic features with BlauS but are usually clinically distinct. These include leprosy, atypical mycobacterial infections, chronic leishmaniasis, orofacial granulomatosis, perioricial dermatitis, granulomatous rosacea, and Crohn's disease.

6 | Treatment Modalities

Systemic corticosteroids (CS) are used as the initial treatment for acute uveitis and arthritis in BlauS. High doses of CS (1–1.5 mg/kg/day, PO or IV) are typically administered during acute flares with tapering to lower doses for maintenance. However, CS alone are often insufficient for long-term disease control, particularly in preventing chronic uveitis and joint damage [1].

Methotrexate (MTX) is one of the most frequently used immunosuppressants in Blau's, especially for managing joint and skin symptoms. Low-dose methotrexate (10–15 mg/m^2 per week, oral or subcutaneous) has demonstrated efficacy in treating musculoskeletal and skin manifestations. However, MTX monotherapy is generally insufficient for long-term disease control, and adjunctive therapies are usually added [1].

Thalidomide is effective for skin, joint, and ocular symptoms, but requires close monitoring for potential side effects, particularly peripheral neuropathy and teratogenicity. In a single-center study of four pediatric patients with BlauS, thalidomide at doses of 1–2 mg/kg in children (with a maximal dose of 50 mg daily) resulted in a 50% efficacy in an aggregate score of clinical severity when measured at 12 months with regards to the reduction of inflammatory markers and clinical symptoms such as fever, rash, or arthritis [22]. Another study of two pediatric patients, a 16-year-old girl and an 8-year-old boy, demonstrated symptomatic improvement with thalidomide, with one patient

TABLE 1 | A proposed treatment approach and algorithm for BlauS, modified from Ferjani et al. (2023) [1].

Manifestation	Skin involvement	Arthritis	Uveitis
First-line therapy	Topical CS	Oral or systemic CS + Methotrexate	Oral or systemic CS + Methotrexate + TNFα inhibitor (Adalimumab or Infliximab) ± Ocular CS injection
Second-line therapy		TNFα inhibitor (Adalimumab or Infliximab)	
Third- and fourth-line therapy		Switch to another TNFα inhibitor (Adalimumab or Infliximab)	
		Switch to an IL-1 inhibitor, IL-6 inhibitor or Tofacitinib	

Abbreviations: CS, corticosteroid; IL, interleukin; TNF, tumor necrosis factor.

TABLE 2 | Levels of evidence for select medications in the treatment of BlauS based on the Strength of Recommendation Taxonomy (SORT).

Agent	Dose	Quality of evidence	Strength of recommendation
Corticosteroids			
Systemic	1–1.5 mg/kg qday PO or IV (acute flares)	2	B
Methotrexate	10–15 mg/m^2 qweek PO or SQ	2	B
Thalidomide	1–2 mg/kg qday (max 50 mg/day)	3	C
Anti-TNFα Agents			
Adalimumab	24 mg/m^2 q2 weeks	3	C
Infliximab	Induction phase: 5 mg/kg every 6–8 weeks for 6 months, OR 3 mg/kg every 8 weeks for 6 months Maintenance phase: 5 mg/kg every 8–12 weeks, OR 3 mg/kg every 12–16 weeks	2	B
IL-1 inhibitor			
Anakinra	3 mg/kg qday SC	3	C
Canakinumab	2 mg/kg qmonth SC	3	C
IL-6 inhibitor			
Tocilizumab	8 mg/kg qmonth IV	3	C
JAK inhibitor			
Tofacitinib	1.7–2.5 mg qday PO	3	C

TABLE 3 | Differential diagnosis of Blau syndrome: Pertinent positives and negatives for clinical decision-making.

Condition	Pertinent positives	Pertinent negatives
Blau syndrome	Triad: granulomatous dermatitis, arthritis, uveitis; early-onset (< 5 years); family history; non-caseating granulomas	No pulmonary involvement; no caseating granulomas; negative TB tests
Juvenile idiopathic arthritis	Arthritis in multiple joints; systemic inflammation; ANA positivity in some subtypes	No granulomas; no uveitis in most cases; no cutaneous granulomatous lesions
Sarcoidosis	Pulmonary involvement; non-caseating granulomas; elevated ACE levels; multi-system involvement	No arthritis in most cases; no familial inheritance; no early childhood onset
Tuberculosis	Pulmonary symptoms; Caseating granulomas; positive TB testing (PPD, IGRA)	No uveitis in most cases; no familial inheritance; no early-onset dermatitis
Early-onset sarcoidosis	Identical to BlauS but lacks family history; early-onset uveitis	No familial inheritance; no systemic arthritis
Granulomatous rosacea	Facial distribution of rash; papulopustular lesions; triggers include sun exposure	No arthritis; no uveitis; no systemic granulomas
Granulomatous Polyangiitis	Upper respiratory and renal involvement; ANCA positivity; systemic vasculitis	No familial pattern; no uveitis; no early cutaneous involvement

experiencing partial restoration of vision after receiving 100 mg thalidomide orally once daily [23].

Anti-TNF-α biologic agents such as adalimumab and infliximab are biologics that are used to treat BlauS. Adalimumab is effective for ocular symptoms and has been successful in preventing vision-threatening uveitis [24]. Although primarily used to target ocular symptoms, adalimumab also decreases granuloma formation, reducing the surface area of the skin eruption and resolving inflammation, as well as alleviating joint symptoms including synovitis. Infliximab has also been shown to be effective at controlling joint and skin symptoms. It also potentially

plays a role in managing ocular symptoms, as a patient with multiple episodes of bilateral uveitis achieved remission when infliximab was added to methotrexate and steroids [25]. The methotrexate dose was reduced and steroids discontinued while on maintenance infliximab. In a separate study of four pediatric patients [26], infliximab normalized inflammatory markers including erythrocyte sedimentation rate and C-reactive protein quickly, with few adverse effects reported. However, disease relapse occurred when dosing frequency was decreased or when methotrexate was discontinued, and financial constraints can be a barrier to accessing treatment.

For patients who fail anti-TNF-α agents, other biologics such as IL-1 inhibitors (e.g., anakinra, canakinumab) and IL-6 inhibitors (e.g., tocilizumab) can be considered. These are promising agents for refractory cases, although they are not as widely studied in BlauS. In one case, a 16-year-old boy with longstanding BlauS had rapid quiescence of severe, resistant panuveitis using canakinumab in combination with prednisone and methotrexate, after failure of response to adalimumab and infliximab [27]. In this patient, there were no major side effects, and he achieved normalization of inflammatory markers. Anakinra, a recombinant IL-1 receptor antagonist (IL-1α and IL-1β), is widely used in other NOD-associated autoinflammatory conditions as a daily injection due to its rapid onset. Some experts consider anakinra a first-line option in BlauS, especially for patients with early and severe inflammatory manifestations. In the literature, the clinical response appears to be variable [1, 28].

Tofacitinib, a pan-Janus kinase (JAK) inhibitor, has potential in patients who fail traditional treatments and/or TNF-α inhibitors. An in vitro study using patient-derived induced pluripotent stem cells demonstrated successful downregulation of STAT1 phosphorylation and inflammatory cytokine production when incubated with tofacitinib [29]. Although tofacitinib did not inhibit the spontaneous NF-κB hyperactivation caused by *NOD2* pathogenic variants, it significantly reduced the expression of NOD2 itself, which prevented further inflammatory cytokine production. Tofacitinib had no impact on pre-existing granulomas, suggesting that its primary benefit lies in preventing ongoing inflammation rather than reversing existing damage. In a case series of three Chinese pediatric patients with Blau syndrome, all with disease onset between 5 and 8 months of age, clinical remission of polyarthritis and marked improvements in laboratory parameters, including ESR, CRP, IL-6, and TNF-α, were achieved with tofacitinib at daily doses ranging from 1.7 to 2.5 mg [30].

Given the complexity and chronicity of BlauS, combination therapy is often required to control both acute and chronic symptoms effectively. Many patients benefit from a combination of CS, methotrexate, and biologics to achieve optimal outcomes. Key therapeutic goals include preventing joint deformities and vision loss, particularly through short-term CS as bridging therapy until more potent agents take effect.

7 | Conclusions

BlauS, a rare autoinflammatory condition driven by *NOD2/CARD15* gain-of-function pathogenic variants, manifests as a triad of granulomatous dermatitis, arthritis, and uveitis, with a risk of blindness if untreated. A granulomatous cutaneous papular eruption is often the first clinical sign of the disease. Skin involvement plays a critical role in early diagnosis but can be misinterpreted as other granulomatous or papular disorders.

While methotrexate remains the standard for joint and skin inflammation, it often fails to control the systemic inflammation. Anti-TNF-α agents like adalimumab and infliximab offer promising results, particularly in preventing vision-threatening uveitis. Adalimumab effectively reduces ocular inflammation, while infliximab shows broader efficacy across joint, ocular, and cutaneous symptoms. However, maintaining remission remains difficult, especially when tapering biologics or discontinuing adjuncts like methotrexate. Emerging treatments, including the JAK inhibitor tofacitinib and thalidomide, have shown effectiveness in refractory cases. Tofacitinib inhibits cytokine overproduction via STAT1, while thalidomide manages systemic inflammation.

Despite advances, further clinical trials and long-term data are needed to optimize management, guiding a personalized approach based on individual characteristics and newer agents' safety profiles. Early recognition of skin involvement may enable timely intervention and reduce morbidity in BlauS.

Author Contributions

Authors made significant contributions to study conception and design, data collection, analysis and interpretation of results, and draft manuscript preparation. All authors read and approved the final version.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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