Molecularly Targeted Therapies for Inflammatory Cutaneous Granulomatous Disorders: A Review of the Evidence and Implications for Understanding Disease Pathogenesis

Erica Hwang[1], Mariam Abdelghaffar[2], Bridget E. Shields[3] and William Damsky[1,4]

Inflammatory cutaneous granulomatous diseases, including granuloma annulare, cutaneous sarcoidosis, and necrobiosis lipoidica, are distinct diseases unified by the hallmark of macrophage accumulation and activation in the skin. There are currently no Food and Drug Administration–approved therapies for these conditions except prednisone and repository corticotropin injection for pulmonary sarcoidosis. Treatment of these diseases has generally been guided by low-quality evidence and may involve broadly immunomodulatory medications. Development of new treatments has in part been limited by an incomplete understanding of disease pathogenesis. Recently, there has been substantial progress in better understanding the molecular pathogenesis of these disorders, opening the door for therapeutic innovation. Likewise, reported outcomes of treatment with immunologically targeted therapies may offer insights into disease pathogenesis. In this systematic review, we summarize progress in deciphering the pathomechanisms of these disorders and discuss this in the context of emerging evidence on the use of molecularly targeted therapies in treatment of these diseases.

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[1]*Department of Dermatology, Yale School of Medicine, New Haven, Connecticut, USA;* [2]*School of Medicine, Royal College of Surgeons in Ireland, Busaiteen, Bahrain;* [3]*Department of Dermatology, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, Wisconsin, USA; and* [4]*Department of Pathology, Yale School of Medicine, New Haven, Connecticut, USA*

Correspondence: William Damsky, Department of Dermatology, Yale School of Medicine, 333 Cedar Street, LCI 501 PO Box 208059, New Haven, Connecticut 06520, USA. E-mail: william.damsky@yale.edu

Abbreviations: BSA, body surface area; CS, cutaneous sarcoidosis; CSAMI, Cutaneous Sarcoidosis Activity and Morphology Instrument; FDA, Food and Drug Administration; FVC, forced vital capacity; GA, granuloma annulare; IHC, immunohistochemistry; NL, necrobiosis lipoidica; PDE4, phosphodiesterase-4; PET-CT, positron emission tomography-computed tomography; PFT, pulmonary function test; PGA, Physician Global Assessment; STAT, signal transducer and activator of transcription; Th, T helper; TYK2, tyrosine kinase 2

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INTRODUCTION

Inflammatory (noninfectious) granulomatous skin diseases include granuloma annulare (GA), cutaneous sarcoidosis (CS), and necrobiosis lipoidica (NL). Although these diseases represent distinct clinical entities, they are unified by often annular clinical lesions and the finding of granulomatous inflammation microscopically, suggesting at least some overlap in their molecular pathogenesis.

Historically, treatments for these diseases have been quite varied and are generally based on low-quality evidence. Development of effective treatments has in part been limited by an incomplete understanding of disease pathogenesis. Indeed, there are no Food and Drug Administration (FDA)–approved therapies for either GA, CS, or NL, recognizing that prednisone (and repository corticotropin injection) is approved for pulmonary sarcoidosis.

In this review, we summarize progress in our understanding of the molecular immunology of these diseases and the implications for developing novel treatment strategies. We also describe the findings of a comprehensive literature review to identify studies evaluating immunologically targeted therapy in these three diseases. Although clinical evidence is still largely limited to case reports and small case series, these observations are helpful for grounding the clinical relevance of evolving immunopathogenic models for each disease and carving the path forward.

LITERATURE REVIEW

A literature review was performed with the search terms [disease] (e.g., GA, sarcoidosis, or NL) AND pathogenesis and [disease] AND treatment. The search was conducted on the PubMed database from inception to October 2022. Articles were screened for relevance by analysis of title and abstract. Only English-language publications were included, and there was no restriction on dates of publication. Reference lists of relevant articles were also analyzed for additional publications, which were included if relevant. The U.S. National Library of Medicine clinical trials database (clinicaltrials.gov) was also queried for relevant studies using the disease entity as the search term.

GA

GA typically presents as dull pink papules and plaques that may be annular (Piette and Rosenbach, 2016). Involvement of the dorsal hands and feet is common, but lesions may

affect other areas and are sometimes widespread. There is a 3:1 female predominance (Barbieri et al., 2021a). Historically GA has not been treated aggressively (if at all), likely for multiple reasons. For example, approximately 50% of cases have been estimated to spontaneously remit within 2 years of onset. However, other patients do not experience spontaneous remission (and if they do, disease can still recur). Furthermore, very little has been known about the QOL impacts of GA. Clark et al. (2023) recently found that GA may have an unexpectedly profound QOL burden in some patients, especially in those with generalized disease. Concern about the possibility of paraneoplastic GA may also be a factor. Finally, for those patients with GA desiring treatment, we do not have high-quality evidence to guide the most appropriate therapy. Indeed, there are no FDA-approved therapies.

Our understanding of GA immunopathogenesis, which is critical for developing effective therapies, has evolved over time. Histologically, GA typically falls into one of two patterns: palisaded or interstitial, with many cases having overlapping patterns. Perivascular lymphocytes are a consistent finding. Several lines of evidence now strongly suggest that GA is a T-cell–dependent cutaneous inflammatory disorder. Studies in the early 2000s showed expansion of specific T helper (Th) 1 polarized CD4+ T cells in GA lesions (Fayyazi et al., 2000; Mempel et al., 2002), and more recently, single-cell RNA sequencing has demonstrated the production of proinflammatory cytokines and chemokines by these cells (Wang et al., 2021). In the clinic, it has been observed that T-cell–stimulating cancer immunotherapies such as anti–PD-1/PD-L1 may trigger or unmask GA, also lending support to this hypothesis (Cornejo et al., 2019). Finally, epidemiologic studies now also demonstrate an association of GA with other autoimmune diseases (but not with solid tumors nor hematologic malignancies) on a population level (Barbieri et al., 2022, 2021b). Together these findings suggest that we may conceptually approach GA treatment in ways similar to the treatment of other inflammatory skin diseases such as atopic dermatitis and psoriasis.

The nature of the underlying immune polarization in GA is not fully clear and requires further study. Although an early study by Fayyazi et al. (2000) suggested Th1 polarization in GA by showing high levels of TNF-α and IFN-γ staining in tissue, Th2 or Th17 cytokines were not evaluated as part of this study, and the methods used may be less robust than newer approaches.

More recent studies also support Th1 polarization (Min et al., 2020; Wang et al., 2021); however, there has been some disagreement among studies about the frequency and magnitude of Th2 polarization in GA. Min et al. (2020) recently examined gene expression in eight cases of GA and found upregulation of both Th1 and Th2 (IL-4 and IL-13) cytokines using RT-qPCR. Wang et al. (2021) recently performed single-cell and bulk RNA sequencing on five GA samples and found Th1 upregulation (IFN-γ and IL-15) without clear upregulation of Th2 cytokine production. The reason(s) for these differential results are not yet clear, and although differences in methodology may play some role, the findings may also suggest a degree of underlying immunologic heterogeneity or overlap in GA. Broader immunophenotyping of GA will be necessary to understand the breadth of molecular heterogeneity in this disease and how it might correlate with distinct clinical and histologic features.

On the basis of current evidence, we propose a working model whereby T cells may recruit monocytes and promote their differentiation to activated macrophages that may alter the extracellular matrix through expression of various

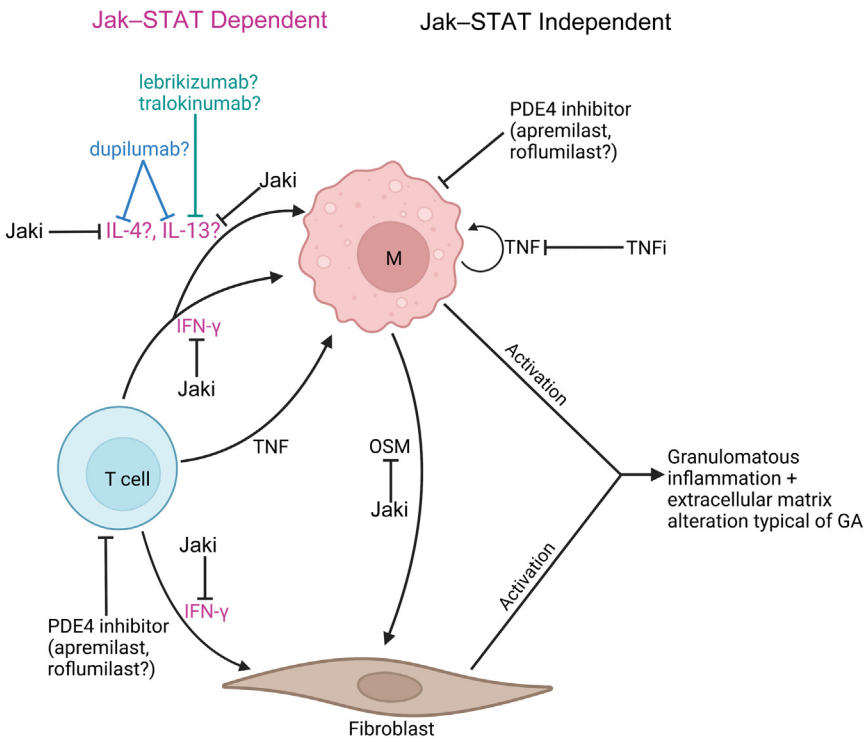

Figure 1. Overview of proposed GA molecular pathogenesis and mechanisms of immunologically targeted therapy. The question mark ? denotes hypothetical and needs further evaluation. GA, granuloma annulare; Jaki, Jak inhibitor; M, macrophage; OSM, oncostatin M; PDE4, phosphodiesterase-4; STAT, signal transducer and activator of transcription; TNFi, TNF inhibitor.

cytokines and stimulation of fibroblasts (Figure 1). The role of tissue-resident memory T cells in GA has not been investigated. Although GA lesions may often recur in the same area, other times, they do not. In the following section, we will review the rationale and evidence for molecularly targeted therapy in GA (Table 1) and how it informs this model.

TNF inhibitors

TNF inhibition has wide-ranging anti-inflammatory effects and was the first molecularly targeted therapy to be evaluated in GA. Chen et al. (2019) recently reviewed the literature regarding the use of TNF inhibitors in GA. They found that 15 of 18 reported patients demonstrated improvement or resolution of GA with adalimumab or infliximab. In the largest observational series of seven female patients treated with adalimumab, all patients improved with an average 85% reduction in body surface area (BSA) involvement. Interestingly, only 20% of patients treated with etanercept responded (see the section on CS for further discussion of etanercept) (Chen et al., 2019).

Since this review by Chen et al. (2019), further cases of GA treated with infliximab, adalimumab, and golimumab have been published. Overall in the literature, 13 of 19 patients (68.4%) treated with adalimumab experienced clearance, with another three improving (Chen et al., 2019; Fanning et al., 2010; Fässler and Schlapbach, 2020; Lam and Hilal, 2022). Four of five patients treated with infliximab (80%) experienced clearance of GA, whereas the fifth experienced a near-complete response (Bürgler et al., 2019; Chen et al., 2019; Fanning et al., 2010). One patient treated with golimumab experienced clearance after 3 months of therapy (Dopytalska et al., 2022).

The source of TNF production in GA is not clear, but macrophages are the most likely contributors, with potential contribution from T cells (Figure 1). One could hypothesize that cases of GA less responsive to TNF inhibition might be relatively more Th2 polarized, but this concept requires further evaluation. Despite the potential promise of TNF inhibitors for treatment of severe GA, high-quality studies are lacking, and a controlled trial is needed to better understand efficacy and safety. Interpretation is also limited by the lack of a validated clinical scoring outcome in GA.

Jak inhibitors

Jak inhibitors can simultaneously inhibit multiple cytokines, including Th1 (IFN-γ and IL-15) and Th2 (IL-4 and IL-13) cytokines, among others (Figure 2). Indeed, multiple studies have shown activation of Jak–signal transducer and activator of transcription (STAT) signaling in GA (Damsky et al., 2020a; Min et al., 2020; Wang et al., 2021), suggesting that Jak inhibition could be a viable approach to treat GA. Proof-of-concept clinical data were published in 2020 by Damsky et al. (2020a) after observing clearance of widespread GA with the broadly acting Jak inhibitor tofacitinib (Jak1/3>2) in a patient with recalcitrant GA. Subsequently, a small prospective open-label study of tofacitinib in five patients (80% female, mean age = 62 ± 5.2 years) with severe GA was performed (Wang et al., 2021). The average disease duration was 10.2 years. The primary outcome was a change in BSA involvement after 6 months of tofacitinib 5 mg twice daily. Three patients had complete clearance of their skin, whereas the other two patients had marked improvement (61 and 70% BSA reduction). In this study, clinical improvement was most closely tied to complete suppression of IFN-γ activity molecularly. In our clinical experience, some patients have exhibited a more robust response to 10 mg tofacitinib twice daily than to 5 mg tofacitinib twice daily. In other patients, 5 mg once daily may be sufficient. Five other case reports in the

Table 1. Targeted Therapies for Granuloma Annulare

Treatment	Molecular Target	Number of Responders/ Number of Patients Treated	References
Adalimumab	TNF-α	16/19	Chen et al., 2019[1]; Fässler and Schlapbach, 2020; Lam and Hilal, 2022
Infliximab	TNF-α	5/5	Bürgler et al., 2019; Chen et al., 2019[1]
Golimumab	TNF-α	1/1	Dopytalska et al., 2022
Tofacitinib (oral)	Jak1/3>2	5/5	Wang et al., 2021[2]
		6/6	Bosch-Amate et al., 2022; Damsky et al., 2020a; Damsky et al., 2020; McPhie et al., 2021
Tofacitinib (topical 2%)	Jak1/3>2	2/2	Damsky and King, 2020; Durgin et al., 2020
		NP/15	NCT05580042[3]
Upadacitinib	Jak1	1/1	Sondermann et al., 2022
Baricitinib	Jak1/2	1/1	Yan et al., 2022
Abrocitinib	Jak1	NP/10	NCT05650736[3]
Apremilast	PDE4	9/9	Bishnoi et al., 2019; Blum and Altman, 2019; Hansel et al., 2021
Dupilumab	IL-4Rα	1/1	Song et al., 2021
Tildrakizumab	IL-23 (p19)	1/2	Awad et al., 2022; Song, 2021b
Ustekinumab	IL-12/IL-23 (p40)	1/1	Song, 2021a

Abbreviations: NP, not published; PDE4, phosphodiesterase-4.
[1]One patient treated with both adalimumab and infliximab.
[2]Prospective single-arm open-label trial.
[3]Pending clinical trial.

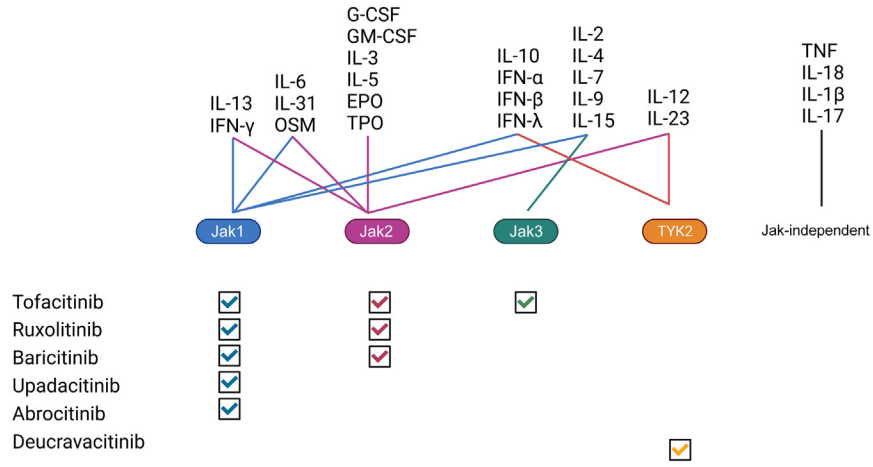

Figure 2. Overview of Jak–STAT-dependent and -independent cytokines of therapeutic relevance. Lines indicate that signal transduction of a cytokine occurs through a given Jak protein. Checked boxes indicate which Jak proteins each Jak inhibitor targets. EPO, erythropoietin; G-CSF, granulocyte colony-stimulating factor; OSM, oncostatin M; STAT, signal transducer and activator of transcription; TPO thrombopoietin; TYK2, tyrosine kinase 2.

literature also describe the benefit of oral tofacitinib in GA: three patients experienced complete resolution, one experienced near complete resolution, and one had a partial response (Bosch-Amate et al., 2022; Damsky et al., 2020a; McPhie et al., 2021).

More recently, more specific Jak inhibitors have been introduced, including Jak1/2- and Jak1-specific inhibitors. Interestingly, IFN-γ, IL-15, IL-4, and IL-13 all signal through Jak1 (Figure 2), suggesting that Jak1-specific inhibition may be sufficient for effective treatment. Proof-of-concept studies have also been published in this area: a patient treated with baricitinib (Jak1/2) and a patient treated with upadacitinib (Jak1) both experienced near-complete resolution of disease (Sondermann et al., 2022; Yan et al., 2022). A study of oral abrocitinib (a Jak1-specific inhibitor) in GA is now underway (NCT05650736).

Given important safety concerns with Jak inhibition, not all patients may be interested in systemic Jak inhibitory therapy. Indeed, not all patients with GA even want treatment at all. That said, other patients are very bothered by their GA, have longstanding disease, have failed a number of commonly used therapies, and are highly motivated to pursue treatment for their GA. In our anecdotal experience, there does not appear a relationship between duration of the disease and likelihood of response to therapy.

As with other inflammatory skin diseases, for patients with localized disease, topical treatment is generally desirable, although very little data on topical Jak inhibition in GA exists. To date, two patients with GA treated with compounded topical 2% tofacitinib ointment showed significant benefit after 12 or 15 weeks of twice-daily application (Damsky and King, 2020; Durgin et al., 2020). Moving forward, drug and vehicle optimization for sufficient dermal penetration will be important and requires future study. Presently, studies with topical AC-1101 2% tofacitinib gel (NCT05580042) and 1.5% ruxolitinib cream (planned) in GA will help to begin to address these questions.

Another important consideration is the boxed warnings for Jak inhibitors, which include thromboembolism, malignancy, and major adverse cardiac events. Jak inhibitors should generally not be used in patients that are smokers (or have extensive past smoking history) or patients with a history of coronary artery disease, hypercoagulability, untreated infections, or active malignancy. For patients with GA interested in embarking on therapy with a Jak inhibitor, appropriate counseling regarding these adverse effects and shared decision making prior to initiation of this (as opposed to other or no) therapy are essential. Future clinical investigation will be important to understand the safety of Jak inhibitors for dermatologic indications compared with that of conventional other immunosuppressants (Daniele and Bunick, 2022) as well as how varying Jak specificities impact these potential adverse effects.

Phosphodiesterase-4 inhibition

Apremilast is a phosphodiesterase-4 (PDE4) inhibitor that downregulates a number of proinflammatory signals by inhibiting downstream NF-κB signaling and promoting anti-inflammatory CREB signaling (Schafer et al., 2014). At the time of our literature review completion, there were nine published reports describing the use of oral apremilast to treat GA. All patients experienced at least partial improvement in a number of lesions, erythema of lesions, and pruritus. Two thirds of these patients had not previously been responsive to topical, systemic, and/or intralesional corticosteroids (Bishnoi et al., 2019; Blum and Altman, 2019; Hansel et al., 2021; Joshi and Tschen, 2021). The exact mechanism of apremilast in GA is not clear but may be related to indirect inhibition of TNF and/or IFN-γ signaling. This observation implies that topical 0.3% roflumilast (another PDE4 inhibitor) cream may be worth evaluating in GA as well. As with other targeted strategies in GA, prospective, controlled studies are needed.

IL-4Rα blockade

Dupilumab inhibits both IL-4 and IL-13 by blocking IL4Rα. Despite the preclinical data implicating Th2 inflammation in GA (Min et al., 2020), there remains only a single reported case on the successful use of dupilumab in GA. Song et al. (2021) treated a female aged 74 years with generalized GA refractory to adalimumab, with dupilumab at atopic dermatitis dosing. The patient had a partial response at 12 weeks. This case is compelling because this patient's GA could be hypothesized to be more Th2 dependent given the failure of TNF inhibition.

GA has also been reported to develop in the setting of dupilumab (Phelps-Polirer et al., 2022). In our group's anecdotal experience, we have not noted significant improvement in patients with GA treated with dupilumab, thus highlighting the need to understand molecular heterogeneity in GA, particularly the functional role of Th2 inflammation, and develop methods to stratify patients on the basis of predominant underlying immune polarization.

IL-17–IL-23 axis inhibition

IL-17 and IL-23 are key drivers of Th17 immunity. The role of these cytokines, if any, has not been well-established in GA. Notably, there are several reports of GA developing on the background of IL-17 inhibitors and no reports of successful treatment of GA with IL-17 inhibition (Bonomo et al., 2017; Clark et al., 2018; Fässler and Schlapbach, 2020; Fox et al., 2020; Gray et al., 2021). IL-17 inhibition may paradoxically promote Th1 immunity in some patients because its inhibition is known to also trigger sarcoidosis or inflammatory bowel disease in some instances (Hornick et al., 2020).

Tildrakizumab inhibits IL-23 (p19 subunit). IL-23 promotes IL-17 production in tissue (Tang et al., 2012). The role of this potential treatment strategy in GA remains unclear. One patient with generalized GA was reported to have no improvement with tildrakizumab after 28 weeks (Song, 2021b). In contrast, Awad et al. (2022) reported improvement in a patient with generalized GA with tildrakizumab after 2 years of treatment, but the report did not describe the kinetics of the response. Ustekinumab, an IL-12/23 (p40 subunit) inhibitor, which can also inhibit Th1 immunity (IL-12) may be another distinct strategy and has been reported to improve GA in a single case (Song, 2021a). The role of tyrosine kinase 2 (TYK2) inhibition, which interferes with IL-12, IL-23, and type I IFN signaling, has not been evaluated in GA. Additional immunologic and clinical evaluation will be needed to further understand any potential role of these strategies in GA.

Summary and future directions

Broader immune characterization of GA across a larger number of cases and clinical morphologies will be a priority moving forward, to better understand the breadth and pattern of immune dysregulation in this disease. Such efforts will inform the likelihood of success of different strategies of targeted immune inhibition in variants of GA, including classic annular papules or plaques, predominantly patch GA, and subcutaneous GA. Individual patients (or specific GA morphologies) may possibly respond better to certain therapies.

Presently, in terms of apparent magnitude and frequency of efficacy, Jak inhibitors appear the most promising. Jak1 inhibition is likely the preferred approach on the basis of molecular and clinical evidence to date; however, Jak3-specific and TYK2 allosteric inhibitors may also merit further evaluation. Controlled trials will be needed to evaluate the efficacy and safety of this approach in GA.

An important consideration beyond active agents is whether topical versus oral approaches are most likely to be successful and how to select patients for studies evaluating one versus the other. As with other inflammatory diseases, BSA involvement is likely key. For patients with BSA involvement of 5–7% or less, topical approaches are likely the most reasonable, whereas in other patients with more widespread involvement (who desire treatment), an oral approach likely has the highest likelihood of success. In GA, where the inflammation is generally dermal predominant, vehicle selection for optimized penetration is also an important consideration. For example, AC-1101 (tofacitinib gel), which contains DMSO to enhance dermal penetration, is undergoing early-stage evaluation (NCT05580042).

There are no validated clinical outcome tools in GA, which would clearly be useful for clinical trials. Clinical assessment tools have been developed and are currently undergoing validation. These include the Granuloma Annulare Severity and Morphology Instrument and Granuloma Annulare-Investigator Global Assessment. Patient-reported outcomes are also important; along these lines, a Patient Global Impression of Change in GA has been developed and is also undergoing evaluation for clinical use. Skin-related QOL metrics are also likely important to include, Skindex-16 being an example.

SARCOIDOSIS

Sarcoidosis can affect any organ. The skin is involved in 16–32% of cases (Grunewald et al., 2019; Rosenbach et al., 2018). CS presents most commonly as pink–red to red–brown papules or plaques, which may be annular and commonly affect the head and neck. However, the cutaneous morphology of sarcoidosis may be varied. The reason for this variability is not well-understood. The effect of CS on QOL has not been intensively studied. In the United States, the United Kingdom, and South Africa, the incidence is highest among Black individuals, who are also more likely to have a chronic disease with inferior outcomes, including higher mortality (Mirsaeidi et al., 2015). The reasons for this racial disparity are still not fully understood but may include socioeconomic factors such as differential exposure to environmental antigens, access to insurance and preventative healthcare, and implicit bias in healthcare interactions (Hena, 2020).

The histologic hallmark of sarcoidosis is the noncaseating granuloma, which is composed of tightly aggregated epithelioid macrophages (Rosenbach et al., 2018). When compared with other causes of cutaneous granulomatous inflammation, sarcoidosis is often described as having naked granulomas—referring to a relative paucity of T cells histologically. Despite this, T cells are thought to be the primary drivers of the disease and are found at the periphery of granulomas (Figure 3).

CD4+ T cells are the predominant lymphocyte type in CS (de Jager et al., 2008). Several lines of evidence suggest that sarcoidosis is a T-cell–dependent disorder, including the association of sarcoidosis with certain HLA alleles, the expansion of specific T-cell subclones in sarcoidosis lesions, disease dynamics in individuals with HIV relating to CD4 counts, and the initiation or unmasking of sarcoidosis by T-cell–stimulating immunotherapies (Wang et al., 2020). General sarcoidosis immunology, which has been most intensively studied in the lung, has been recently reviewed (Drent et al., 2021).

Judson et al. (2012) used microarrays to compare gene expression in 15 lesional sarcoidosis skin biopsies with that in five healthy controls. The authors found marked upregulation of *IL12*, *IFNG* (and *STAT1*), as well as *TNF* in CS relative to that in the controls. Interestingly, significant *IL17A*

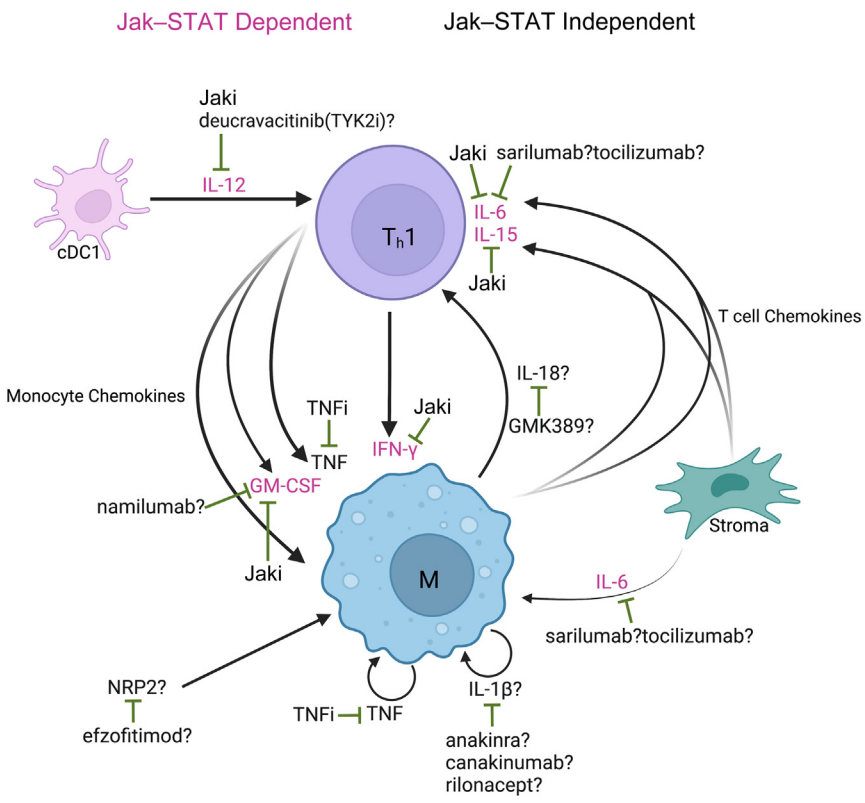

Figure 3. Overview of proposed cutaneous sarcoidosis molecular pathogenesis and mechanisms of immunologically targeted therapy. The question mark *?* denotes hypothetical and needs evaluation. cDC, conventional dendritic cell; Jaki, Jak inhibitor; M, macrophage; STAT, signal transducer and activator of transcription; Th1, T helper cell 1; TNFi, TNF inhibitor; TYK2i, tyrosine kinase 2 inhibitor.

and *IL17F* expression was not found in CS. The lack of definitive IL-17 axis cytokines in CS is notable, given the implication of putative Th17.1 cells (which produce IFN-γ and may coproduce or have previously produced IL-17) in pulmonary sarcoidosis (Drent et al., 2021). Whether this is a true biologic difference or reflects differences in methodology is not yet clear.

Th2 cytokines have been implicated in pulmonary sarcoidosis and may play a role in fibrotic manifestations of the disease (Drent et al., 2021). Any potential changes in Th2 cytokines were not shown in Judson et al. (2012)'s study on gene expression in CS. mTOR signaling, which may be activated downstream of cytokine, metabolic, and other signals, has also been implicated in sarcoidosis and is supported by a mouse model of granulomatous inflammation induced by constitutive mTOR activation in the myeloid lineage (Crouser et al., 2021; Damsky et al., 2018; Linke et al., 2017).

The only FDA-approved therapies for sarcoidosis are approved for pulmonary sarcoidosis and include prednisone and repository corticotropin injection. Prednisone remains the recommended first-line systemic therapy on the basis of the latest European Respiratory Society consensus guidelines, though this is a provisional recommendation owing to very low-quality available evidence (Baughman et al., 2021). There are no FDA-approved therapies specifically for CS. Current evidence for targeted treatments for both internal organs and CS are reviewed below (Table 2).

TNF-α inhibitors

TNF-α inhibitors are commonly used off label to treat sarcoidosis, including CS, and may be used in patients requiring high steroid doses and/or who have failed other immunosuppressants such as methotrexate. For patients where severe CS is the driving motivation for treatment, TNF inhibition may be the first systemic therapy employed, owing to the potential adverse effects of systemic glucocorticoids and frequent chronicity of the disease.

Prospective, randomized studies. Baughman et al. (2006) performed a double-blind randomized controlled trial in 138 patients with chronic corticosteroid-dependent pulmonary sarcoidosis treated with either 3 mg/kg or 5 mg/kg infliximab (n = 93) for six treatments over 24 weeks compared with placebo (n = 45). Patients treated with infliximab experienced significant improvement in forced vital capacity (FVC) compared with those who received a placebo ($P = 0.038$), which was the primary outcome measure. Subgroup analysis of patients with skin involvement (n = 36) treated with infliximab (n = 26) showed a nonsignificant ($P = 0.087$) trend toward improvement in a skin-specific severity score compared with those who received a placebo (n = 8) (Judson et al., 2008). A subsequent posthoc analysis (Baughman et al., 2016) from the same trial evaluated 17 participants with chronic facial skin involvement and found improvement of induration ($P = 0.009$ at week 24) but not of erythema or the involved area in the patients treated with infliximab (n = 12) compared with those who received a placebo (n = 5).

Pariser et al. (2013) conducted a double-blind, randomized, placebo-controlled trial of adalimumab 40 mg weekly (n = 10) versus placebo (n = 6) comparing the change in CS after 12 weeks with the Physician Global Assessment (PGA) of the overall volume of cutaneous lesions. Four of 10 treated

Table 2. Targeted Therapies for Sarcoidosis

Treatment	Molecular Target	Number of Responders/ Number of Patients with Internal Disease	References	Number of Responders/Number of Patients with Cutaneous Disease	References
Adalimumab	TNF-α	9/11	Sweiss et al., 2014[1]	5/10[2] → 10/13[1] (includes eight from randomized phase)	Pariser et al., 2013[3]
				NS/5	Heidelberger et al., 2017
Infliximab	TNF-α	NS/93	Baughman et al., 2006[2]	NS/26	Judson et al., 2008[4]
		NS/56	Vorselaars et al., 2015[1]	7/12	Baughman et al., 2016[4]
		26/31	Sakkat et al., 2022	27/29 + NS/40	Heidelberger et al., 2017; Sakkat et al., 2022; Stagaki et al., 2009; Vorselaars et al., 2015
Golimumab	TNF-α	NS/42	Judson et al., 2014[2]	9/17	Judson et al., 2014[2]
Ustekinumab	IL-12/IL-23 (p40)	NS/46	Judson et al., 2014[2]	3/21	Judson et al., 2014[2]
Tofacitinib (oral)	Jak1/3>2	6/9	Damsky et al., 2022[1]	10/10	Damsky et al., 2022[1]
		3/5	Friedman et al., 2021[1]	10/10	Damsky et al., 2020b; Dopytalska et al., 2022 (includes Damsky et al., 2018; Kerkemeyer et al., 2021; Talty et al., 2021
		14/14	Collaborative group: MI(6) study group, 2022; Damsky et al., 2020b; Kerkemeyer et al., 2021; Zhang et al., 2021		
Tofacitinib (topical 2%)	Jak1/3>2			2/2	Alam et al., 2021; Singh et al., 2021
Ruxolitinib	Jak1/2	3/3	Levraut et al., 2019; Rotenberg et al., 2018; Wei et al., 2019	2/2	Rotenberg et al., 2018; Wei et al., 2019
Baricitinib	Jak1/2	1/1	Scheinberg et al., 2020		
Abrocitinib	Jak1			NP/10	NCT05696795[5]
Sirolimus	mTOR	3/3	Gupta et al., 2020; Kelleher et al., 2020; Manzia et al., 2011		
Efzofitimod	Neurolipin-2	25	Culver et al., 2023		
		NP/264	NCT05415137[5]		
Namilumab	GM-CSF	NP/30	NCT05351554[5]		
CMK389	IL-18	NP/66	NCT04064242[5]		
Anakinra	IL-1 receptor	NP/28	NCT04017936[5]		

Abbreviations: NS, not specified; NP, not published; PGA, Physician Global Assessment.
[1]Prospective single-arm open-label trial.
[2]Randomized controlled trial.
[3]Responders defined as PGA scores decreasing from 4 to ≤2.
[4]Different subset analyses of the same original trial, likely overlap in patients.
[5]Pending clinical trial.

patients had clearance or marked improvement after 12 weeks. After an additional 12-week open-label phase, 8 of 13 evaluable patients were clear or had marked improvement.

Judson et al. (2014) conducted a randomized controlled trial comparing golimumab (a TNF inhibitor; 100 mg every 4 weeks) with ustekinumab (an IL-12/IL-23 inhibitor; 90 mg every 8 weeks) and placebo in 173 patients with chronic pulmonary sarcoidosis and/or CS; the primary outcome was change in FVC at 16 weeks. At week 16, no significant differences were observed in change in FVC with ustekinumab or golimumab compared with placebo. Nine of 17 patients (52.9%) with CS treated with golimumab improved as assessed with PGA at 28 weeks, but this was not statistically significantly better than the improvements in those who received the placebo (30% also improved).

Sweiss et al. (2014) conducted an open-label prospective study of 11 patients with refractory pulmonary sarcoidosis treated with 40 mg adalimumab weekly for 45 weeks. Of 11 patients who underwent treatment, 9 had improvement in FVC, improvement in 6-minute walk distance, and/or reduction in immunosuppressive therapy by 24 weeks. Vorselaars et al. (2015) conducted an open-label prospective cohort study of 56 patients with refractory fluorodeoxyglucose-positron emission tomography–positive sarcoidosis treated with infliximab (5 mg/kg every 4 weeks), resulting in marked improvement in mean pulmonary function parameters after 6 months of treatment. Changes in cutaneous involvement with treatment were not well-delineated in the Sweiss et al. (2014)'s and Vorselaars et al. (2015)'s publications.

Retrospective studies. Several studies have also looked retrospectively at TNF inhibition in CS. Stagaki et al. (2009) retrospectively reviewed 116 treatment courses in 54

patients with lupus pernio at their institution. They found that infliximab-containing regimens (5 mg/kg every 6 weeks) with or without corticosteroids resulted in resolution or near resolution of lupus pernio lesions in 77% (10 of 13) of those treated and were superior to all other regimens, including other corticosteroid-containing regimens. Subsequent cohorts have also shown an overall steroid-sparing effect of infliximab, including in patients with CS patients (Sakkat et al., 2022).

Heidelberger et al. (2017) retrospectively analyzed 46 patients with CS who were treated with infliximab (n = 40), adalimumab (n = 5), or etanercept (n = 1) first line, with 14 patients receiving subsequent courses of anti-TNF therapy. Thirteen patients (28.3%) achieved complete clearance of their cutaneous lesions, and another 18 (39.1%) had a partial cutaneous response. Ten patients discontinued treatment owing to adverse effects. These authors found a steroid-sparing effect of TNF inhibition (Sakkat et al., 2022).

Etanercept is a fusion protein of TNFR2 and IgG Fc that has a mechanism of action somewhat distinct from those of other TNF inhibitors. Etanercept was investigated in pulmonary sarcoidosis, but the study was terminated early owing to excessive treatment failures (Utz et al., 2003). Etanercept also has negative trial data in ocular sarcoidosis (Baughman et al., 2005).

The differential efficacy of etanercept compared with that of other TNF inhibitors is biologically interesting. One possible explanation may result from structural differences: etanercept's composition includes two soluble TNF receptors, which is unique compared with other TNF inhibitors, which are mAbs against TNF. Etanercept—TNF complexes are known to be relatively unstable (when compared with those of mAbs), allowing dissociation of TNF. In addition, adalimumab and infliximab exhibit complement-dependent cytotoxicity and thus can lyse cells that express TNF on their surface, whereas etanercept cannot (Mitoma et al., 2018). Although these differences have not been evaluated in CS, they are compelling in the setting of the clinical data, and in our opinion, etanercept use should be avoided in sarcoidosis.

In summary, although there is clearly an important role for TNF inhibition in the management of CS, use remains off label. Data in the prospective setting appear less robust than typical clinical use and retrospective studies might suggest. Infliximab (5 mg/kg every 6 weeks after loading) and adalimumab (40 mg weekly after loading) have the greatest apparent efficacy. Infliximab may remain the preferred agent given the ability to dose higher; in our practice, it is not uncommon to use higher doses, including 10 mg/kg, to clear the skin and then downtitrate the dose.

Apremilast

Aprelimast is an oral PDE4 inhibitor approved for psoriasis. In 2012, Baughman et al. (2012) published the results of a study evaluating apremilast in patients with CS. In this study, 15 patients with CS who were on an otherwise stable immunosuppressive regimen were treated with 20 mg apremilast twice daily (slightly lower than the current FDA approved dose of 30 mg twice daily) and evaluated for a change from baseline in skin severity after 12 weeks of treatment. After 12 weeks, though there was a statistically significant reduction in induration scores, erythema and area of involvement were unchanged. Apremilast has largely not been pursued as a therapeutic target in sarcoidosis since this time.

IL-12/23 inhibitors

Given the role of IL-12 in promoting IFN-γ and Th1 immunity and its marked upregulation in CS (and sarcoidosis in general), there was optimism that the IL-12/IL-23 (p40) inhibitor ustekinumab might be effective (Judson et al., 2012). In the Judson et al. (2014)'s trial discussed earlier, the ustekinumab group was followed for a primary outcome related to their pulmonary sarcoidosis, but PGA change at 16 weeks was a secondary outcome in patients with cutaneous involvement. Only 3 of 21 patients (14.3%) with CS improved, compared with 30% of placebo-treated and 53% of golimumab-treated patients. Pulmonary outcomes with ustekinumab were also disappointing. The reason for this is somewhat unclear given the important role of IL-12 in induction of IFN-γ responses by lymphocytes but could relate to dosing or the potential relative importance of p35 versus p40 subunit targeting in the inhibition of IL-12. IL-23—specific (p19) inhibitors have not been formally evaluated in sarcoidosis. The role of TYK2 inhibition, which interferes with IL-12, IL-23, and type I IFN signaling, has not been evaluated in sarcoidosis. Interestingly, therapy with recombinant IFN-β can sometimes trigger the development of sarcoidosis.

IL-17 inhibitors

IL-17 inhibitors also have not been formally evaluated in sarcoidosis. In fact, there are reports of IL-17 unmasking or triggering inflammatory granulomatous disorders, including sarcoidosis (Hornick et al., 2020). Interestingly, inflammatory bowel disease, including Crohn's disease (which can also have granulomas), can also unmask or worsen under IL-17 inhibitor treatment (Hueber et al., 2012; Orrell et al., 2018; Targan et al., 2016). Although the frequency and mechanism of this occurrence in sarcoidosis are not fully understood, it likely involves redirection of immunity through IFN-γ (Th1 immunity) when IL-17 (Th17 immunity) is inhibited, which is a well-described phenomenon. For this reason, we avoid the use of IL-17—specific inhibitors in patients with sarcoidosis.

mTOR inhibition

Following preclinical evidence that mTOR activation in macrophages might promote granuloma formation in mice, there was significant excitement that mTOR inhibition could be a promising treatment approach for patients with sarcoidosis. There have been a few cases reported in which sirolimus (mTORC1 inhibitor) has demonstrated efficacy in patients with sarcoidosis (Gupta et al., 2020; Kelleher et al., 2020; Manzia et al., 2011). A clinical trial at the Medical University of Vienna (Vienna, Austria) investigating oral and/or topical sirolimus for pulmonary sarcoidosis and CS appears to have been prematurely terminated in 2021 (which may be related to either enrollment, efficacy issues, or another reason); we await any publication describing the results (2018). Altogether, although mTOR activation appears common in sarcoidal granulomas, it remains unclear whether it is a secondary characteristic of activated macrophages or a primary driver of disease.

Efzofitimod

NRP2 is a transmembrane receptor that is highly expressed on immune cells and may play roles in migration, antigen presentation, and phagocytosis (Schellenburg et al., 2017). NRP2 is expressed on macrophages in culture as well as in sarcoidosis granulomas from the lung and skin. Efzofitimod (ATYR1923) is a fusion protein of an immunomodulatory histidyl-tRNA synthetase domain and human IgG1 that binds to NRP2 and modulates its activity.

An early-phase randomized placebo-controlled trial (NCT03824392) investigated the efficacy of efzofitimod at dosages of 1 mg/kg (n = 8), 3 mg/kg (n = 8), and 5 mg/kg (n = 9) in patients with pulmonary sarcoidosis taking stable doses of prednisone. The primary outcomes were safety and tolerability, and the secondary outcomes were steroid-sparing effects over the study duration and changes in pulmonary function tests (PFTs) over 24 weeks. Efzofitimod was found to be safe and well-tolerated. There was a slight but dose-dependent reduction in prednisone dose with efzofitimod and a similar slight improvement in pulmonary function parameters at higher doses (Culver et al., 2023). Patients in the 5 mg/kg group had statistically significant improvement in patient-reported pulmonary measures. A follow-up placebo-controlled phase 3 trial is ongoing to further investigate the safety and efficacy of efzofitimod (3 mg/kg or 5 mg/kg) in patients with pulmonary sarcoidosis taking corticosteroids, with a primary outcome measure of steroid-sparing ability after 48 weeks of treatment (NCT05415137). Should this drug continue to move forward, it would be interesting to examine cutaneous outcomes in patients with skin involvement.

Jak inhibitors

Several cytokines implicated in CS, including type I IFNs (IFN-α/β), IFN-γ, IL-6, IL-12, IL-23, and GM-CSF, signal through the Jak–STAT pathway (Figure 2). Depending on the specificity of the Jak inhibitor employed, some or many of these cytokines could be simultaneously inhibited. IL-18, which has also been implicated in sarcoidosis and is an emerging possible therapeutic target, does not signal through the Jak–STAT pathway (Shigehara et al., 2001). IL-18 is also known as IFN-γ–inducing factor, and so Jak inhibition could conceivably indirectly inhibit the downstream effect of IL-18. Other cytokines such as IL-17 and TNF also do not signal directly through Jak–STAT. However, TNF is known to be strongly induced by IFN-γ in the setting of granulomatous inflammation (Kindler et al., 1989), and so its production (rather than its function) is inhibited by Jak inhibitors.

Damsky et al. (2018) evaluated 21 CS biopsy samples with immunohistochemistry (IHC) to detect Jak–STAT pathway activation in tissue and found that all samples were strongly positive for activated (phosphorylated and localized to the nucleus) STAT1 downstream of IFN-γ as well as STAT3 downstream of IL-6 and other cytokines. In particular, phosphorylated STAT1 staining was strongest in the core of granulomas, suggesting the importance of IFN-γ in this area. Interestingly, phosphorylated STAT3 staining was strongest in between granulomas, as opposed to within them; the significance of this observation is not clear. A similar pattern was seen in pulmonary sarcoidosis tissue samples, and the pattern was highly reproducible among samples (Damsky et al., 2020a). Using gene expression analysis, Judson et al. (2012) also found upregulation of *IL12*, *IFNG*, *TNF*, and *STAT1*, which is also indicative of a Th1 immune response and highly consistent with the STAT staining signature that was observed using IHC. The results are consistent with those of prior studies with PBMCs and other tissues from patients with sarcoidosis (Judson et al., 2012; Li et al., 2016; Rosenbaum et al., 2009; Zhou et al., 2017, 2012).

In 2018, Damsky et al. (2018) reported the first published case of a patient with cutaneous and pulmonary sarcoidosis treated with oral 5 mg tofacitinib (a Jak1/3>2 inhibitor) twice daily who experienced complete clinical and histologic clearance of her cutaneous disease. Around the same time, Rotenberg et al. (2018) reported the first case of a patient with multiorgan sarcoidosis treated for Jak2-sequence variant polycythemia vera with the Jak1/2 inhibitor ruxolitinib who experienced complete resolution of her CS and dramatic improvement in lung involvement by chest imaging and PFTs. These initial reports generated excitement about the possibility of this therapeutic option.

Subsequent case reports have also demonstrated clinical benefit for both cutaneous and pulmonary sarcoidosis with Jak inhibitors, including tofacitinib (n = 23), ruxolitinib (n = 3), and baricitinib (n = 1) (Collaborative group: MI(6) study group, 2022; Damsky et al., 2020a, 2020b, 2018; Friedman et al., 2021; Kerkemeyer et al., 2021; Levraut et al., 2019; Rotenberg et al., 2018; Scheinberg et al., 2020; Talty et al., 2021; Wei et al., 2019; Zhang et al., 2021). Overall, 13 patients have been assessed for cutaneous disease, and 20 have been assessed for internal disease. Eleven of 13 (84.6%) patients experienced complete or near-complete resolution of their CS, with the other 2 (15.4%) patients experiencing partial response. Nine of 20 (45%) patients experienced complete or near-complete resolution of their internal disease, and the remaining 11 (55%) showed partial response. Two additional case reports showed partial improvement in CS with compounded 2% tofacitinib ointment (Alam et al., 2021; Singh et al., 2021).

Despite the promise of these observations, there is likely bias in case reports toward cases where patients responded positively to the treatment. Furthermore, because Jak inhibition with varying specificity has been reported, it has remained unclear what the key cytokine targets (and thus the key Jak proteins) are in sarcoidosis. To this end, Damsky et al. (2022) recently published a proof-of-concept, prospective study evaluating the use of 5 mg tofacitinib twice daily in the treatment of 10 patients with sarcoidosis with cutaneous involvement. Of the 10 patients, 9 had internal organ involvement. In this open-label study, the primary outcome was a change in the Cutaneous Sarcoidosis Activity and Morphology Instrument (CSAMI) score, a measure of CS severity, after 6 months of treatment. Secondary outcomes included change in internal organ disease activity as assessed by whole-body positron emission tomography-computed tomography (PET-CT) and immunologic correlates in skin and blood. Patients were allowed to discontinue or taper baseline prednisone at the investigators' discretion if they improved.

All 10 patients had improvement in their cutaneous disease with a mean reduction in disease activity of 82.7%, and 6 patients experienced a complete response (CSAMI score

reduced to 0). Whole-body PET-CT (total lesional glycolysis) showed that of the nine patients with internal organ involvement, three patients experienced >98% reduction in disease activity, and another two had at least a 50% reduction in disease activity. However, a weakness of this study was that PFTs were not captured as a function of treatment. Two patients who responded only partially were later treated with higher doses of tofacitinib (up to 10 mg twice daily) and experienced further improvement in both CS and internal organ involvement, conceptionally illustrating dose dependency in the response and suggesting that some patients may require a higher dose for maximal efficacy.

Molecular analysis of lesional skin and blood samples from patients before and after tofacitinib showed that changes in an *IFNG* transcriptional signature tracked most closely with clinical improvement. Indeed, canonical targets of IFN-γ, CXCL9, and CXCL10 are also elevated in the blood of patients with pulmonary sarcoidosis and correlate with disease severity, with CXCL10 also correlated with disease course (Arger et al., 2020); CXCL11 correlates with lung function testing parameters and symptoms of dyspnea (Arger et al., 2019).

In the open-label trial, *TNF*, *GMCSF*, *IL12*, *IL15*, and *IL6* transcriptional activity also correlated with responses, supporting the roles of these cytokines in disease pathogenesis (Damsky et al., 2022). CS molecular pathogenesis is summarized in Figure 3.

A key question moving forward is which Jak proteins should be prioritized for inhibition in CS (and sarcoidosis in general), given the number of Jak inhibitors with varying specificity now approved (Figure 2). IFN-γ (Jak1/2) appears paramount. IL-6 (Jak1/2) and IL-15 (Jak1/3) may also be important and share Jak1 dependency. GM-CSF signals through Jak2 and is an important macrophage activation factor. IL-12 signals through Jak2/TYK2. The degree to which Jak2 inhibition and/or TYK2 inhibition adds efficacy beyond Jak1 inhibition in sarcoidosis is still unclear. A clinical trial of the Jak1-specific inhibitor, abrocitinib, in sarcoidosis (NCT05696795) will be informative. Larger controlled trials are undoubtedly needed to better assess the efficacy and safety of Jak inhibition in this disease. As discussed earlier, Jak inhibitors have boxed warnings for severe infection, major adverse cardiovascular events, thrombosis, and malignancy, and so developing safety data on these agents in sarcoidosis is also very important.

IL-6 inhibition

IL-6 is another cytokine that has been of therapeutic interest in sarcoidosis. A report by Sharp et al. (2019) described four patients with sarcoidosis treated with tocilizumab (an IL-6R inhibitor). In this retrospective case series, tocilizumab appeared to provide benefit in patients who had failed other steroid-sparing therapies, including TNF inhibition. One of the four patients had skin involvement and was reported to have a significant reduction in size, nodularity, and erythema of the CS lesions. Another case report described the use of tocilizumab in a patient with Blau syndrome (Lu et al., 2018). Interestingly, there are multiple instances in the literature describing the development of sarcoidosis or sarcoidosis-like disease in patients receiving IL-6 inhibitors, including tocilizumab (Lambert et al., 2021; Theodosiou et al., 2020).

A placebo-controlled pilot clinical trial of sarilumab (another IL-6R inhibitor) in 15 patients with glucocorticoid-dependent sarcoidosis has been completed (NCT04008069); however, the results have not yet been posted or published. The results of this study should be interesting and should shed some light on the potential for IL-6–specific inhibition in this disease.

Other targets

A clinical trial to investigate namilumab, an inhibitor of GM-CSF, has been initiated in pulmonary sarcoidosis and aims to enroll 100 patients in a phase 2, placebo-controlled study (NCT05314517). The primary outcome of this study is the proportion of subjects requiring rescue treatment for worsening sarcoidosis from baseline to 26 weeks. Secondary outcomes will include PFTs and QOL metrics. This trial will provide important information on the role of GM-CSF in sarcoidosis.

A novel IL-18 inhibitor (CMK389) is also under investigation in chronic pulmonary sarcoidosis in a phase 2 placebo-controlled study that aims to enroll 66 patients (NCT04064242). Patients will be evaluated for a primary outcome of change in FVC after 16 weeks of treatment. To what extent stimulation of IL-18 (also known as IFN-γ–inducible factor) is required for an ongoing production of IFN-γ after the disease is initiated remains unclear, but whether or not CMK389 is efficacious will undoubtedly help to answer this question.

Anakinra, an IL-1 inhibitor, is being trialed in patients with cardiac sarcoidosis in a phase 1 randomized clinical trial where it will be compared with standard of care (NCT04017936). Patients will be evaluated for change in CRP plasma concentration after 4 weeks of treatment, with several secondary outcome measures of cardiac disease also evaluated. Interestingly there are some case reports of patients developing sarcoidosis or sarcoidosis-like disease in the setting of anakinra therapy (Friedman and English, 2018; Sacre et al., 2013).

Summary and future directions

Similarly to GA, a priority moving forward in sarcoidosis is broader immune characterization across more cases and clinical morphologies. Given the often-varied presentation of CS, a better understanding of phenotype–immunologic correlation will be particularly important. Comparing how closely immune dysregulation is correlated between different organ sites (e.g., skin vs. lung) in the same individual is also important and will help us to most rationally inform new therapeutic approaches.

Jak inhibitors represent an exciting development in the treatment of CS, though the quality of the data remains limited. TNF inhibitors may also have very meaningful efficacy, and the quality of the evidence in CS is superior with TNF inhibitors. However, preclinical data suggests that in sarcoidosis, TNF production occurs downstream of IFN-γ (Jak1/2), and so, at least conceptually, Jak inhibition of IFN-γ may represent the most proximal and potent strategy (Damsky et al., 2022). Understanding how Jak1-specific inhibitors compare with more broadly acting Jak inhibitors,

such as tofacitnib and ruxolitinib, will be key. Whether or not allosteric TYK2 inhibitors may be a viable approach has not been investigated. Planned clinical studies, including those with GM-CSF (Jak2) or IL-6 (Jak1/2) inhibition in sarcoidosis, will provide important information on the clinical importance of these other Jak–STAT-dependent cytokines.

As discussed earlier with GA, some patients with localized CS may be more well-suited for topical therapy. However, unlike GA, most patients with CS also have systemic disease, which also typically influences treatment selection.

For CS, recent trials have used CSAMI as an efficacy outcome measure. Sarcoidosis has additional complexity where changes in disease activity in other organs are also important in assessing response. This is further nuanced given the heterogeneous clinical presentation of sarcoidosis and varied patterns/extent of internal organ involvement. For pulmonary sarcoidosis, pulmonary function testing parameters have typically been used for primary outcomes in clinical trials. There is a lack of consensus on the best outcome measure, with others suggesting that imaging methods to assess disease activity (e.g., PET-CT) and/or biomarkers may also be useful in a clinical trial setting. Development of consensus around optimal outcomes will be very important moving forward. Incorporation of patient-related outcomes into studies is also key, with QOL measures extending beyond the skin (e.g., King's Sarcoidosis Questionnaire and Fatigue Assessment Scale). Finally, given the varied presentation of sarcoidosis and the challenge of a unifying clinical outcome measure, development of circulating and/or tissue biomarkers of disease activity will be helpful.

NL

NL is a granulomatous skin condition that predominately affects the lower extremities and is characterized by well-demarcated pink–red to yellow papules and plaques that may show ulceration over time (Reid et al., 2013). Ulceration, which is painful, occurs in about one third of patients. Histologic examination reveals pan-dermal involvement with horizontal tiers of palisading histiocytes surrounding layers of degenerated extracellular matrix (Rosenbach et al., 2018).

The pathogenic mechanisms of NL are still under active investigation. NL is commonly—but not always—seen in the setting of diabetes mellitus (either type 1 or type 2) (Reid et al., 2013). Immunohistochemical studies of NL by Wakusawa et al. (2013) showed significant infiltration of CD163-positive macrophages. IL-17 staining was variably observed, suggesting an inflammatory mechanism (Wakusawa et al., 2013). Kato et al. (2014) subsequently demonstrated infiltration of CD4+ T cells greater than that of CD8+ T cells throughout the dermis, findings arguing for a primarily inflammatory etiology, with T cells playing some role in the disorder. Our group found constitutive activation of STAT1 and STAT3 through IHC studies in 11 NL specimens, again supporting an inflammatory etiology and suggesting that Jak–STAT-dependent cytokines play a role (Damsky et al., 2020c). The field still has a long way to go in understanding NL immunomechanisms.

Molecularly targeted treatments

Although exploration of immunologically targeted treatments for NL is in its infancy (Table 3), TNF-α inhibitors have the largest body of evidence supporting their use. Since 2003, multiple case reports have been published with infliximab (systemic administration, n = 5; intralesional administration, n = 3), adalimumab (n = 1), and etanercept (n = 2), primarily for ulcerative NL (Barde et al., 2011; Basoulis et al., 2016; Cummins et al., 2004; Drosou et al., 2003; Fertitta et al., 2019; Hu et al., 2009; Kolde et al., 2003; Nunes de Mattos et al., 2019; Suárez-Amor et al., 2010). No clinical trials have been performed with TNF-α inhibitors in NL. Of the 11 patients treated with a TNF-α inhibitor reported in the literature, all but one had ulcerative NL prior to treatment, and all 11 experienced at least partial response in parameters such as re-epithelialization, reduction in erythema or induration, and

Table 3. Targeted Therapies for Necrobiosis Lipoidica

Treatment	Molecular Target	Number of Responders/ Number of Patients Treated	References
Infliximab (systemic)	TNF-α	5/5	Basoulis et al., 2016; Fertitta et al., 2019; Drosou et al., 2003; Hu et al., 2009; Kolde et al., 2003
Infliximab (intralesional)	TNF-α	3/3	Barde et al., 2011
Adalimumab	TNF-α	1/1	Nunes de Mattos et al., 2019
Etanercept		2/2	Cummins et al., 2004; Suárez-Amor et al., 2010
Oral tofacitinib	Jak1/3>2	4/4	Damsky et al., 2020c; Erfurt-Berge and Sticherling, 2020; Janßen and Jansen, 2022; McPhie et al., 2021
Baricitinib	Jak1/2	1/1	Barbet-Massin et al., 2021
Ruxolitinib (oral)	Jak1/2	1/1	Lee and English, 2018
Ruxolitinib (topical)	Jak1/2	NP/12	NCT04492618[1]
Ustekinumab	IL-12/IL-23 (p40)	3/3	Beatty et al., 2021; Hassoun et al., 2017; Pourang and Sivamani, 2019
Secukinumab	IL-17A	NP/18	NCT03791060[1]
PCS499	likely PDE	NP/4	NCT04800562[1]

Abbreviations: NP, not published; PDE, phosphodiesterase.
[1]Pending clinical trial.

reduction of functional impairment. Three of these patients experienced complete remission of their disease, with marked improvement in another six of the cases.

Ustekinumab, which inhibits IL-12 and IL-23, has also been reported as a targeted treatment for NL in three case reports, with reported improvement in inflammatory symptoms, including ulceration (Beatty et al., 2021; Hassoun et al., 2017; Pourang and Sivamani, 2019). Ustekinumab may target both the Th1 and Th17 pathways by inhibition of IL-12 and IL-23, respectively (Hassoun et al., 2017).

An open-label study evaluating secukinumab (IL-17A inhibitor) in NL was initiated in 2019 and aimed to enroll 18 participants (NCT03791060). However, the study was halted prematurely owing to the COVID-19 pandemic and did not resume.

Several case reports of Jak inhibition in NL have also been published. Five patients with ulcerative NL and one patient with nonulcerative NL have been treated with oral Jak inhibitors, including tofacitinib (Jak1/3>2) (n = 4), ruxolitinib (Jak1/2) (n = 1), and baricitinib (Jak1/2) (n = 1) (Barbet-Massin et al., 2021; Damsky et al., 2020c; Erfurt-Berge and Sticherling, 2020; Janßen and Jansen, 2022; Lee and English, 2018; McPhie et al., 2021). All five of the patients with ulcerative NL experienced closure of their ulcerations and improvement in inflammation, and the patient with nonulcerative NL experienced complete remission. One patient on tofacitinib who continued to have surrounding inflammatory plaques after ulcer healing subsequently improved with the addition of intralesional triamcinolone, to which her disease had previously been refractory (Damsky et al., 2020c). In this case, IHC of the skin after treatment with tofacitinib revealed mitigation in Jak–STAT signaling but unremitted NF-κB staining, suggesting that Jak–STAT-independent cytokines (such as TNF) might have been sustaining the disease while on the tofacitinib. After addition of intralesional corticosteroids, staining for NF-κB activation was essentially negative.

An open-label study of 1.5% ruxolitinib cream in 12 patients with NL was recently completed (NCT04492618). The primary outcome was a change in the mean NL lesion score from baseline to week 12. Eleven patients completed the study. On the basis of the results section of the clincialtrials.gov listing, there appears to be a statistically significant finding; we await the publication of the results of this exciting study.

DURATION OF THERAPY AND TRIAL DESIGN

We are frequently asked how long patients with GA, CS, and NL need to be treated. As with other inflammatory dermatologic disorders, we view molecularly targeted therapy in inflammatory granulomatous disorders as a treatment, not a cure. Just as in a patient with psoriasis treated with a biologic, if therapy is withdrawn, we would generally expect a recurrence of the disease. However, some patients can achieve sustained remission off therapy (Yee, 2023). We often counsel patients considering Jak systemic therapy regarding the not-uncommon necessity for chronic therapy. Once disease is controlled, we generally try to taper the dose, and sometimes a trial off drug entirely is indicated and can be successful; but more often than not disease recurs when the drug is stopped. Developing biomarkers to guide questions around the need for ongoing therapy will be important.

In our experience using Jak inhibitors specifically in CS and GA, our anecdotal experience is that although most patients recur when therapy is tapered or stopped, occasionally, patients can sustain disease-free remission off therapy. How treatment affects the natural course of the disease is still unclear. We are presently embarking on molecular studies to try to understand why some patients recur and others do not and the divergent molecular and/or T cell memory mechanisms that may underlie these patterns.

As noted throughout, well-designed controlled clinical trials are needed. Randomized, blinded placebo-controlled studies largely have not been performed in these diseases and will be essential to delineate the safety and efficacy of any new therapy. Thus, educating and partnering with industry collaborators that have the resources to embark on such studies will be key.

In our experience designing smaller open-label trials in GA and CS, we have aimed to include patients who may have longstanding disease (>2-year duration) to reduce the likelihood of spontaneous remission during the study. We have observed that patients with even longstanding disease (>10 years) can respond well to effective therapy, and so typically, we do not have an upper limit for disease duration in terms of enrollment. Granulomatous disorders may be slow to improve even with effective therapy, so study durations of 3–4 or preferably even 6 months may be needed to best define efficacy. As discussed earlier, disease-relevant, validated clinical scoring tools and patient-reported outcomes and QOL metrics should all be included.

GA and CS are diseases that do have clinical and, to some extent, histologic heterogeneity, as discussed earlier. How this correlates with molecular heterogeneity and potentially to response to a targeted therapy is not well understood. Incorporation of microscopic and molecular studies on lesional skin before and after therapy will be useful strategies for linking clinical heterogeneity with immunologic changes and treatment response patterns.

CONCLUSION

Noninfectious granulomatous skin disorders are a diverse set of cutaneous inflammatory diseases that are unified by the hallmark characteristic of macrophage accumulation and activation in affected tissue. Recent insights into their pathogenic mechanisms help elucidate the optimal molecular targets of treatment for each disease. In this review, we discussed the pathogenesis and current use of targeted treatments in GA, CS, and NL. Our review underscores the need for robust controlled trials to better evaluate the efficacy of promising therapies, including Jak inhibitors, TNF-α inhibitors, and various other mAbs and immunomodulatory molecules. Further studies will not only add therapeutic tools to our arsenal but also have the potential to enhance our understanding of the pathogenesis of noninfectious granulomatous skin diseases.

The key findings from this review include the following:

1. Evidence for therapies in GA, CS, and NL mostly consists of case reports and small case series, with few prospective studies.

2. TNF inhibitors, including adalimumab and infliximab, have the most support for efficacy, but the quality of evidence remains low.
3. Jak inhibitors have yielded promising results in these diseases, but larger controlled studies are needed to generate a higher quality of evidence.
4. Several additional targeted therapies are actively being investigated, especially in CS, and together with the growing knowledge of disease immunomechanisms herald the beginning of a new era in the treatment of these diseases.

Data availability statement

No datasets were generated or analyzed during this study.

ORCIDs

Erica Hwang: http://orcid.org/0000-0002-5728-9875
Mariam Abdelghaffar: http://orcid.org/0009-0001-7643-0061
Bridget E. Shields: http://orcid.org/0000-0002-5734-0167
William Damsky: http://orcid.org/0000-0003-0975-4071

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Conceptualization: EH, WD; Data Curation: EH; Writing – Original Draft Preparation: EH, MA, BES, WD; Writing – Review and Editing: EH, MA, BES, WD

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