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Review

Macrophage Polarization in Sarcoidosis: Implications for Granuloma Formation, Fibrosis, and Therapeutic Strategies

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ABSTRACT

Sarcoidosis is a multisystem granulomatous disease with a complex and incompletely understood immunopathogenesis. Macrophages and T lymphocytes play pivotal roles in granuloma formation and disease progression through dynamic interactions involving cytokine signaling and immune regulation. Recent evidence suggests that macrophage polarization, particularly the balance between classically activated M1 macrophages and alternatively activated M2 macrophages, plays a critical role in inflammatory granuloma formation and fibrotic progression in pulmonary sarcoidosis. TH1-related cytokines, including interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), promote proinflammatory M1 polarization, whereas TH2-related cytokines, such as interleukin (IL)-4 and IL-13, drive M2 polarization, tissue remodeling, and fibrosis. Emerging transcriptional, single-cell spatial transcriptomic, and 3D organoid studies further demonstrate the remarkable heterogeneity of macrophages in sarcoid granulomas. Current and emerging therapeutic approaches, including corticosteroids, methotrexate, anti-TNF agents, leflunomide, Janus kinase inhibitors, and novel macrophage-targeted strategies (such as efzofitimod), may exert their effects, in part, by modulating these distinct macrophage activation pathways. This review summarizes the available evidence on macrophage polarization in sarcoidosis and provides an immunology-informed clinical framework for disease endotyping, biomarker-guided monitoring, and targeted therapeutic strategies to prevent fibrotic progression.

KEYWORDS: Macrophage polarization, sarcoidosis, granulomatous inflammation, pulmonary fibrosis, immunopathogenesis

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INTRODUCTION

Sarcoidosis is a multisystem disease with unknown etiology and pathobiology.[1] Although there is considerable progress in understanding its genetic, epigenetic, environmental, and immunologic context,[2,3] the exact mechanisms underlying disease initiation and progression remain incompletely understood.[2,4] Recent evidence suggests that dysregulated innate and adaptive immune responses, together with persistent antigenic stimulation, contribute to granuloma formation and chronic inflammation.[5-7] The pathologic hallmark of sarcoidosis is the formation of noncaseating epithelioid granulomas associated with CD4+ T-cell infiltration.[8] This granulomatous reaction involves macrophages, multinucleated giant cells, CD8+ T cells, B cells, and occasionally neutrophils and eosinophils.[6,9,10] Furthermore, recent transcriptomic and bronchoalveolar lavage (BAL) studies have highlighted the important role of activated macrophage subsets and cytokine networks in granuloma maintenance and fibrotic progression.[11]

Immunopathogenesis of Sarcoidosis

Granulomas are dynamic interactions between macrophages and T lymphocytes. This granulomatous response is mainly driven by a TH1 cytokine network, including but not limited to interleukin (IL)-2, interferon-gamma (IFN-γ), and tumor necrosis factor (TNF)—which downstream promotes the recruitment of inflammatory cells via IFN-γ-inducible chemokines such as CXCL9 and CXCL10—[5,7]-and it is often supported in clinical practice by biomarkers such as sIL-2R and angiotensin-converting enzyme, although neither is specific enough to be used alone.[9,12-14] More recent evidence also suggests that Th17 cells and related cytokines, including IL-17 and IL-23, play a role in maintaining chronic granulomatous

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inflammation and disease progression.[15,16] T cells effectively regulate induction, functional differentiation, survival, and metabolic reprogramming of macrophages.[17,18]

Macrophage Polarization in Sarcoidosis

Unlike T-cell polarization, macrophage polarization demonstrates considerable plasticity, and M1 (classical) and M2 (alternative) activation states exist on a functional continuum rather than as distinct populations. In fact, these phenotypes are dynamic and highly reversible under the influence of cytokines, tissue microenvironment, metabolic pathways, and cellular interactions.[19,20] Recent single-cell transcriptomic studies have further demonstrated significant heterogeneity among granuloma-associated macrophages in sarcoidosis.[21]

The authors also believe this, supported by relatively recent evidence that granuloma formation is caused by an immunologic response to a persistent or poorly degradable antigen.[22,23] Recent studies have further suggested that microbial antigens, autoantigens, and dysregulated host immune responses may all contribute to persistent granulomatous inflammation in sarcoidosis.[24,25] Although monocyte polarization toward M1 or M2 macrophages could progress in the absence of T cells,[26] in most circumstances, it is generally thought that Th1 and Th2 cells push monocytes toward M1 and M2 macrophages.[27,28] This interaction between macrophages and T cells is critical in the crosstalk between innate and adaptive immunity. Activation and recruitment of monocytes and macrophages by TH1 and TH2 cells may lead to progression toward either cellular immunity or a fibrotic outcome.[27,29] Furthermore, recent evidence suggests that macrophage metabolic reprogramming and local tissue hypoxia may influence granuloma persistence and fibrosis.[30,31] After granuloma formation, T-cell activation may be associated with down-regulation or a shift from TH1 toward TH2 immunity. Activated TH2 cells induce IL-10 release, which suppresses the production of proinflammatory cytokines. In the presence of IL-4, IL-13, and IL-21, polarization toward the M2 macrophage phenotype promotes expression of non-opsonic receptors such as CD163 and CD206.[22,32] Moreover, increased expression of CD163+ and CD206+ on macrophages in pulmonary sarcoidosis granulomas has been demonstrated in human tissue studies.[22]

Evidence of M2 Macrophages in Human and Experimental Models

There are few studies addressing macrophage polarization in humans with sarcoidosis.[22,33,34] Although the exact characterization of macrophage phenotypes and their pathways of involvement remains difficult, partly because identifying an ideal animal model is challenging,[35] accumulating evidence supports the remarkable heterogeneity of macrophages in sarcoid granulomas. Recent advances in transcriptomic and single-cell sequencing technologies have further demonstrated diverse macrophage subpopulations associated with inflammatory and fibrotic phenotypes.[31,36]

To assess this phenotypic continuum in tissue samples more accurately, advanced imaging methods—such as Quantum Dot-conjugated antibody labeling—now enable highly sensitive multiplex imaging of co-expressed M1 (e.g., CD80/CD86) and M2 (e.g., CD163/CD206) markers in human and *in vitro* granulomatous lesions.[37,38] Using an innovative *in vitro* model, treatment of peripheral blood mononuclear cells (PBMCs), isolated from sarcoidosis patients, with polystyrene beads coated with purified protein derivatives (PPD) induced the formation of multicellular granuloma-like aggregates and alternatively activated macrophages (M2).[39,40] Beyond single-cell suspensions *in vitro*, 3D organoid and co-culture platforms further elucidate the microenvironmental drivers of polarization. Interactions between macrophages, fibroblasts, and extracellular matrix components in these 3D systems drive a rapid phenotypic switch from an early M1 inflammatory response toward M2 polarization and promote the fusion of macrophages into multinucleated giant cells.[37,41] This model was associated with an IL-13–regulated gene expression pathway and with a decreased IFN-γ/IL-13 ratio in PBMC responses to PPD. Furthermore, these findings support the hypothesis that aberrant macrophage polarization contributes to persistent granulomatous inflammation and fibrosis.[22,39,40]

Macrophages and Fibrotic Progression

M2 polarization also appears to be present in fibrotic lung disorders. The study demonstrated that elevated concentrations of CCL18 in BAL fluid were associated with the extent of fibrosis in interstitial lung disease (ILD).[42] In the study by Pechkovsky et al.,[43] M2 macrophages were identified based on cytokine production and flow cytometric phenotyping using anti-CD206 antibodies, providing evidence for M2 polarization in fibrotic lung disease. Recent studies have further suggested that alternatively activated macrophages play a role in extracellular matrix remodeling, fibroblast activation, and progressive pulmonary fibrosis through production of profibrotic mediators such as transforming growth factor-beta (TGF-β) (and its downstream effector connective tissue growth factor), CCL18, and PDGF;[44] in sarcoidosis, these pathways may be associated with local fibrotic remodeling around chronic granulomatous lesions, although the precise causal links are not yet fully defined.[37,45] Moreover, macrophage-driven fibrotic pathways may represent a potential therapeutic target in chronic pulmonary sarcoidosis with fibrotic progression (Figure 1).[46]

In sarcoidosis granulomas, M2 macrophage activation is uniquely characterized by increased expression of CD163—which specifically distinguishes sarcoidosis from tuberculosis (TB) lymphadenopathy—and increased expression of CCL18, which is associated with progressive fibrosis.[22,47] IL-4 and IL-13 promote M2 polarization through STAT6 signaling and may also contribute to the formation of multinucleated giant cells, which are a key feature of sarcoid granulomas.[7,39]

Therapeutic Implications and Emerging Therapies

Conventional initial therapy primarily targets proinflammatory pathways associated with M1 macrophages.[48,49] Corticosteroids

Main Points

- Macrophage plasticity and cytokine signaling are important components of sarcoidosis immunopathogenesis.

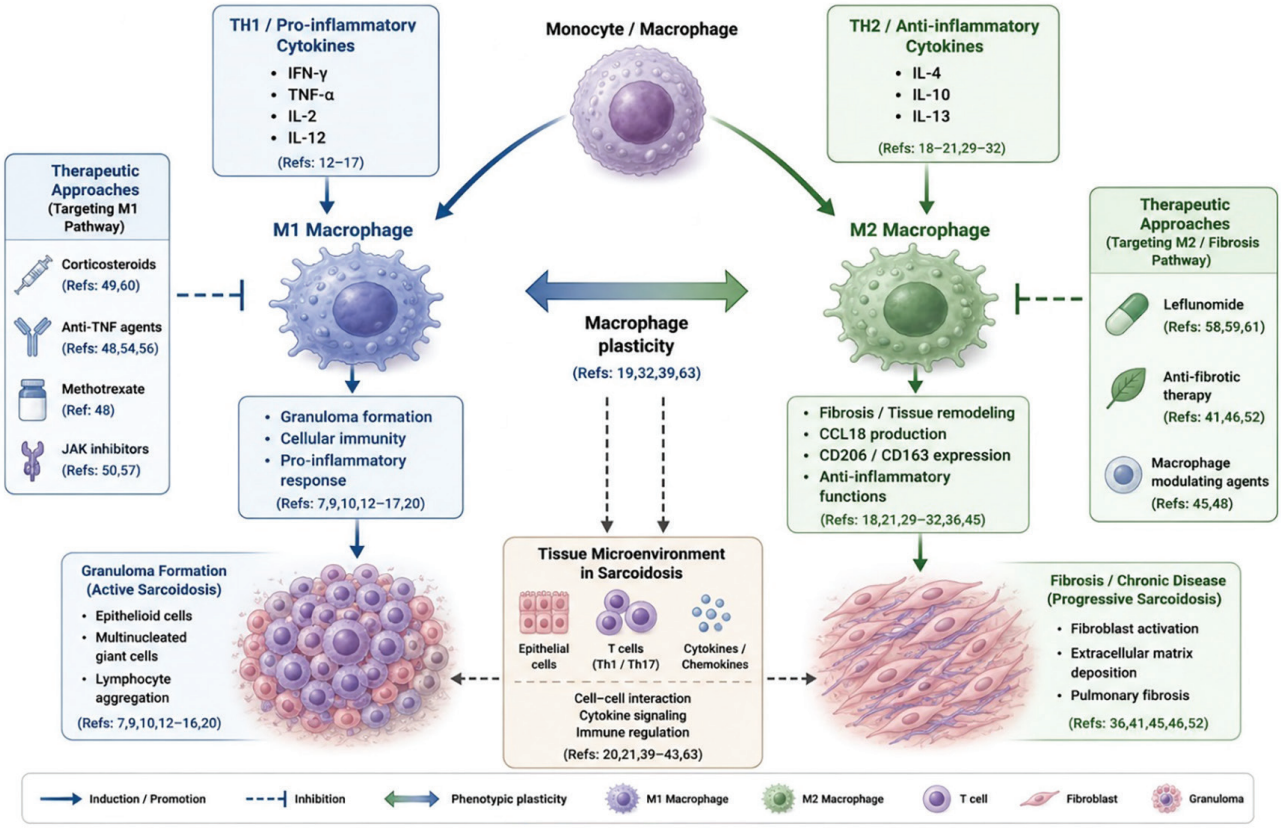


Figure 1. Dynamic macrophage polarization in sarcoidosis. Schematic overview of M1 and M2 macrophage polarization in sarcoidosis, demonstrating their role in granuloma formation, inflammation, fibrosis, and potential therapeutic targets

(CS) and conventional immunosuppressive agents primarily suppress inflammatory cytokine signaling, including the TNF-α and IFN-γ pathways, and are the cornerstone of sarcoidosis therapy. However, increasing evidence suggests that persistent M2 polarization may contribute to chronic fibrosis and irreversible organ damage. Therefore, therapeutic agents that modulate the activity of profibrotic macrophages and prevent excessive M2-induced tissue remodeling could be an important strategy for preventing fibrotic progression. Recent studies have also highlighted the potential role of Janus kinase (JAK)/STAT inhibitors, anti-fibrotic therapies (including nintedanib and pirfenidone, which are established in other progressive ILD,[50,51] and macrophage-targeted immunomodulatory approaches in refractory or fibrotic sarcoidosis.[52-54] Ultimately, current expert opinion suggests that effective treatment of sarcoidosis should involve balanced modulation of both M1 and M2 polarization states rather than suppression of a single immune pathway, which can be operationalized through an immunology-based clinical workflow (Figure 2).[48]

CS are generally considered first-line therapeutic agents that exert rapid and potent anti-inflammatory effects. CS are known to modulate the NF-κB signaling pathway and suppress the production of proinflammatory cytokines, including IFN-γ and TNF-α.[55] Although CS are highly effective in short-term disease control, their long-term benefit in preventing disease progression and pulmonary fibrosis remains uncertain. Furthermore, there is no convincing evidence that long-term corticosteroid therapy improves survival. Recent studies also suggest that chronic corticosteroid exposure may contribute to immune dysregulation and infectious complications.[56,57] Methotrexate (MTX), commonly used as a second-line agent in the treatment of sarcoidosis, inhibits TNF-α release through adenosine A2A receptor signaling while potentially increasing IL-4 and IL-13 expression, creating a microenvironment that may favor M2 macrophage polarization.[55,58] Nevertheless, the relationship between MTX-induced immunomodulation and fibrotic progression in sarcoidosis remains incompletely understood and requires further investigation. In recent years, biologic therapies targeting TNF-α, as well as JAK/STAT signaling inhibitors, have emerged as promising therapeutic approaches for refractory sarcoidosis.[7,54,59]

Partial blockade of IFN-γ as a therapeutic strategy for sarcoidosis may also shift M1 macrophages toward an inactive M0 state. Although granulomatous inflammation may be controlled in this situation, impaired cellular immunity could increase susceptibility to infections and malignancies. Inhibition of STAT6 phosphorylation may suppress M2 polarization and consequently reduce fibrotic progression.[60] Targeting the IL-13/STAT6 axis offers a novel therapeutic avenue to halt M2-mediated fibrotic progression; in particular, preclinical inhibition of STAT6 in PBMCs significantly inhibits granulomatous nodule formation and suppresses M2 polarization.[7,33,39] Leflunomide, through modulation of these signaling pathways, has shown beneficial effects in improving lung function and controlling pulmonary fibrosis in some patients with sarcoidosis.[61]

Current therapeutic strategies in sarcoidosis primarily target inflammatory pathways associated with macrophage and T-cell

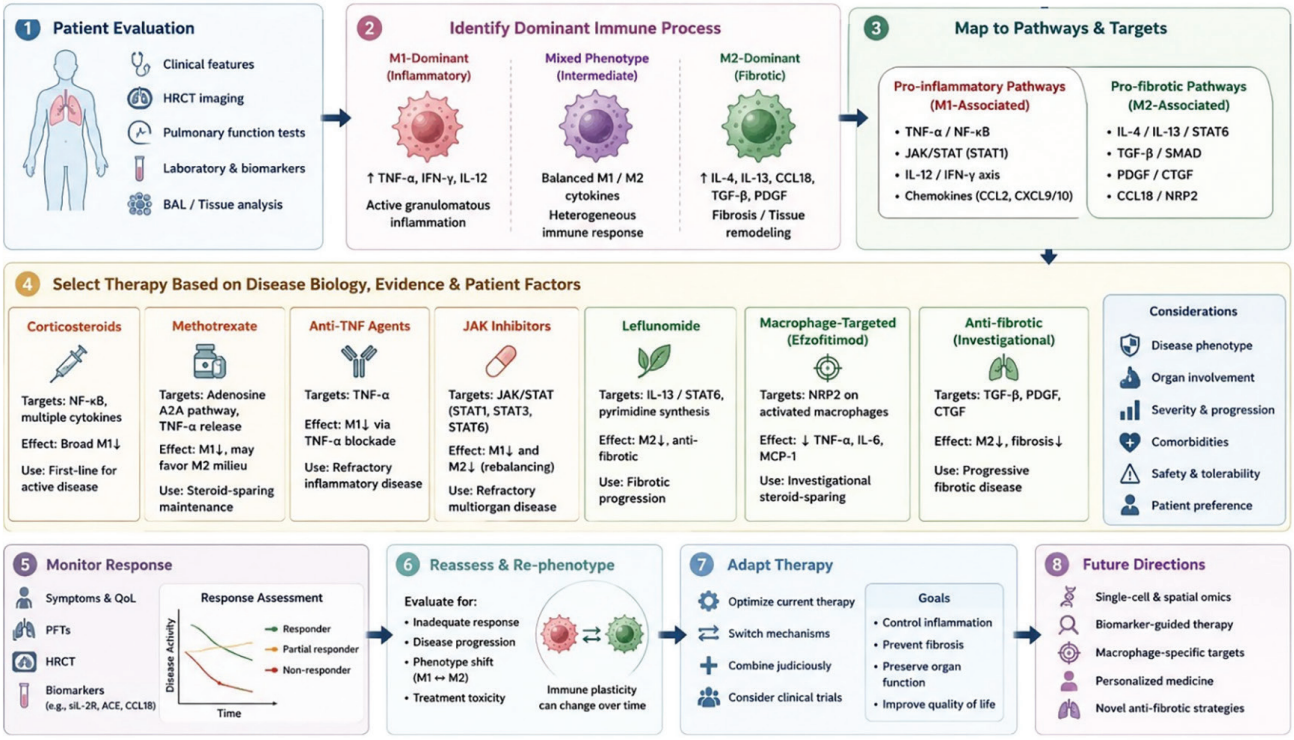


Figure 2. A conceptual framework for immunology-based therapeutic reasoning and phenotype-based medicine in pulmonary sarcoidosis

(1) Baseline diagnostic and longitudinal evaluation integrating clinical parameters, HRCT, PFTs, BAL analysis, and patient-reported QoL metrics. **(2, 3)** Stratification of disease endotypes based on immunopathogenetic mechanisms into M1-dominant (pro-inflammatory), mixed, or M2-dominant (profibrotic) macrophage phenotypes, alongside their respective chemokine/cytokine networks (e.g., CXCL9/10, CCL2, TGF-β, CTGF, and CCL18). **(4)** Mapping molecular endotypes to targeted therapeutic interventions, including immunomodulatory agents and anti-fibrotic therapies. **(5–8)** Comprehensive response monitoring using established adjunctive serum biomarkers (e.g., sIL-2R and ACE), investigational markers of macrophage activation and profibrotic activity (e.g., CCL18), and functional and radiological assessments to track disease activity, immune plasticity, and potential fibrotic progression.

ACE: angiotensin-converting enzyme, BAL: bronchoalveolar lavage, CTGF: connective tissue growth factor, HRCT: high-resolution computed tomography, PFTs: pulmonary function tests, QoL: quality of life, sIL-2R: soluble interleukin-2 receptor, TGF-β: transforming growth factor-beta

activation. CS remain the first-line therapy and suppress key proinflammatory mediators including the NF-κB, IFN-γ, and TNF-α signaling pathways.[7] MTX and leflunomide are commonly used steroid-sparing agents with additional immunomodulatory effects on macrophage polarization and cytokine regulation. Anti-TNF biologic agents, such as infliximab and adalimumab, have shown clinical benefit in refractory sarcoidosis by suppressing granuloma-associated inflammatory signaling. However, anti-TNF therapy carries a known risk of serious infections, including reactivation of TB, necessitating careful screening before treatment.[62,63] More recently, JAK inhibitors, including tofacitinib, have emerged as promising therapeutic approaches by modulating cytokine-mediated macrophage and T-cell activation pathways. Although these therapies may effectively control granulomatous inflammation, over-suppression of immune responses may increase susceptibility to infection or alter macrophage homeostasis.

In addition, targeted therapies that affect intracellular signaling alter macrophage function; mTOR inhibitors (e.g., sirolimus) reverse the metabolic reprogramming and aerobic glycolysis that promote the transformation of macrophages into giant cells. JAK/STAT inhibitors suppress both STAT1-mediated M1 inflammation and STAT3-mediated M2 persistence, thereby offering a two-pronged approach to resolving refractory granulomas.[7,64,65] Therefore, future therapeutic strategies may increasingly focus on the balanced modulation of macrophage polarization and the prevention of fibrotic progression rather than the isolated suppression of a single inflammatory pathway.[55,56,66,67] Finally, emerging macrophage-targeted therapies are designed to complement, rather than simply replace, systemic immune suppression by selectively modulating macrophage function. In theory, reprogramming prefibrotic macrophages toward a repair phenotype may reduce chronic granulomatous inflammation and slow fibrotic progression (Table 1).[15,68]

Among the emerging therapeutic options, efzofitimod is noteworthy because it offers a more targeted approach to immune modulation and may be particularly relevant to the pathobiology of sarcoidosis.[69-71] In contrast to conventional therapies that broadly suppress inflammation, efzofitimod has been investigated as a potential steroid-sparing strategy in pulmonary sarcoidosis, which could be very tempting because it may affect monocyte-macrophage activation pathways that are involved in persistent granulomatous inflammation.[70,71] Efzofitimod selectively targets neuropilin-2, which is overexpressed in activated granulomatous macrophages, and induces an anti-inflammatory program that reduces the expression of macrophage CD14 and key cytokines (TNF-α, IL-

Table 1. Macrophage polarization in sarcoidosis and related therapeutic implications

Macrophage phenotype/pathway	Main cytokines or markers	Major immunologic role	Association with sarcoidosis	Potential therapeutic approaches
M1 macrophage polarization	IFN-γ, TNF-α, IL-2, IL-12	Pro-inflammatory response, granuloma formation, cellular immunity	Active granulomatous inflammation and chronic immune activation	Corticosteroids, anti-TNF agents, methotrexate, JAK inhibitors
M² macrophage polarization	IL-4, IL-10, IL-13, CD163, CD206, CCL18	Tissue remodeling, immune regulation, and profibrotic activity	Associated with chronic pulmonary sarcoidosis and fibrotic progression	Leflunomide and other pathway-modulating approaches; potential macrophage-directed and antifibrotic strategies
Th1/Th17-mediated immune response	IFN-γ, IL-17, IL-23, T-bet/ RORγT	Maintenance and amplification of granulomatous inflammation	Persistent granuloma formation and chronic inflammation	Corticosteroids, anti-TNF agents, JAK inhibitors, and other targeted immunomodulatory approaches
Granuloma-associated macrophage heterogeneity	Mixed and overlapping macrophage phenotypes; IL-13-regulated pathways; tissue-specific transcriptional signatures	Dynamic macrophage plasticity and granuloma maintenance	May contribute to variable disease phenotypes, chronic inflammation, and disease progression	Precision immunomodulation, cytokine-targeted therapy, and future macrophage-directed strategies
Fibrosis-associated macrophage activity	CD206, CCL18, TGF-β, PDGF	Fibroblast activation, extracellular matrix remodeling, and tissue fibrosis	Associated with progressive fibrotic pulmonary sarcoidosis	Antifibrotic approaches and modulation of macrophage-associated profibrotic pathways
JAK/STAT-associated signaling	JAK/STAT pathway; STAT6-related signaling	Regulation of cytokine responses and macrophage activation; potential influence on inflammatory and profibrotic pathways	Emerging mechanistic and therapeutic relevance in refractory and chronic disease	JAK inhibitors; promising but requiring further sarcoidosis-specific clinical evidence
Emerging immunomodulatory therapies	Cytokine and macrophage-associated inflammatory pathways	Modulation of persistent inflammation and macrophage-mediated immune responses	Potential relevance to refractory or progressive pulmonary sarcoidosis	Anti-TNF biologics, JAK inhibitors, efzofitimod, and other emerging targeted therapies

IFN-γ: interferon-gamma, TNF-α: tumor necrosis factor-alpha, IL: interleukin, JAK: Janus kinase, TGF-β: transforming growth factor-beta, PDGF: platelet-derived growth factor

6, MCP-1), thereby suppressing granulomatous fibrosis without causing widespread immunosuppression.[69,72] Although clinical evidence is limited and the drug is still in the investigational phase, its development represents a broader shift toward therapies that aim to modulate disease-driving immune cell programs, rather than simply reduce inflammation globally (Table 2).[7,69]

Although current sarcoidosis therapies primarily suppress inflammation in a broad and indirect manner, future therapeutic strategies may move toward more selective modulation of pathogenic macrophage programs, including activation status, phenotype change, cytokine responsiveness, and profibrotic signaling.[5,7] This concept is supported by early clinical observations in sarcoidosis, such as JAK-STAT inhibition with tofacitinib, which was associated with improvement in long-term multi-organ disease—as routinely tracked by changes in high-resolution computed tomography, pulmonary function tests, BAL parameters, and patient-reported quality of life metrics[73-76]— and by broader macrophage-based therapeutic research in chronic inflammatory conditions.[54,67] However, much of the mechanistic and therapeutic literature on direct targeting of macrophages has not emerged from sarcoidosis-specific studies but rather from research in other inflammatory or fibrotic disease models. Accordingly, these approaches should be considered promising translational avenues rather than currently established sarcoidosis therapies.[68,77] However, the precise effects of macrophage-mediated immunomodulation on long-term disease progression remain incompletely understood and require further investigation. Recent therapeutic approaches have increasingly focused on targeted immune modulation, including anti-TNF biologics and JAK inhibitors, particularly for refractory and chronic fibrotic sarcoidosis.[66,67]

Recent advances in immunology, transcriptomic, and single-cell technologies have significantly improved our understanding of macrophage heterogeneity and immune dysregulation in sarcoidosis.[9,78] Emerging evidence suggests that granuloma-associated macrophages display dynamic and tissue-specific phenotypes that contribute not only to inflammation but also to fibrosis and chronic disease progression.[34,36] These findings have opened new perspectives for precision medicine and macrophage-targeted therapeutic strategies. Future therapeutic approaches may increasingly rely on individualized immune profiling, targeted cytokine modulation, and selective inhibition of pathogenic signaling pathways involved in macrophage activation and fibrotic remodeling.[79,80] Although

Table 2. Current and emerging therapeutic options in sarcoidosis and their effects on macrophage polarization

Drug/class	Main target/ pathway	Effect on macrophage polarization	Clinical setting	Level of evidence in sarcoidosis	Main limitations/safety concerns
Corticosteroids	NF-κB, broad proinflammatory cytokines (TNF-α, IFN-γ)	Broad M1↓; indirect effects on M^2	First-line for symptomatic pulmonary and extrapulmonary sarcoidosis	Guideline-supported; extensive clinical experience	Long-term toxicity (metabolic, bone, infectious risk); uncertain benefit on fibrosis
Methotrexate	Adenosine A2A receptor signaling; TNF-α release; may increase IL-4/IL-13	M1↓; may favor M^2 microenvironment via IL-4/IL-13	Second-line steroid-sparing agent; chronic pulmonary and cutaneous disease	Guideline-supported; RCTs and observational studies	Hepatotoxicity, cytopenias, pulmonary toxicity; requires monitoring
Anti-TNF agents (infliximab, adalimumab)	TNF-α neutralization	M1↓ via TNF-α blockade	Refractory pulmonary, cutaneous, neurologic, and cardiac sarcoidosis	Guideline-supported; RCTs (infliximab) and multiple series	Infectious risk (TB reactivation), infusion reactions, cost
Leflunomide	IL-13/STAT6 axis; pyrimidine synthesis	M^2↓ via STAT6 inhibition; may reduce profibrotic activity	Chronic pulmonary sarcoidosis with fibrotic progression; steroid-sparing	Observational studies; small trials	Hepatotoxicity, GI side effects, teratogenicity
JAK inhibitors (tofacitinib, baricitinib)	JAK/STAT signaling (STAT1, STAT3, STAT6)	M1↓ and M^2↓ (rebalancing of both arms)	Refractory multiorgan sarcoidosis, especially cutaneous and pulmonary disease	Case series, small observational studies; systematic reviews	Infectious risk, VTE, lipid abnormalities, cytopenias; long-term safety in sarcoidosis not fully defined
Efzofitimod	Neuropilin-2 (NRP2) on activated granulomatous macrophages	Selective modulation of activated macrophages; reduces M1 cytokines (TNF-α, IL-6, MCP-1)	Investigational steroid-sparing therapy in pulmonary sarcoidosis	Phase 1b/2a and Phase 3 trials (ongoing)	Still investigational; long-term efficacy and safety under evaluation
Anti-fibrotic approaches (e.g., nintedanib, pirfenidone – investigational in sarcoidosis)	Profibrotic pathways (TGF-β, PDGF, CTGF)	M^2↓ and profibrotic macrophage activity↓ (theoretical in sarcoidosis)	Considered in progressive fibrotic lung disease; sarcoidosis-specific data limited	Preclinical and extrapolated from IPF/CTD-ILD; sarcoidosis-specific evidence limited	Limited sarcoidosis-specific data; cost and side effects (GI, hepatic, photosensitivity)

IFN-γ: interferon-gamma, TNF-α: tumor necrosis factor-alpha, IL: interleukin, TB: tuberculosis, JAK: Janus kinase, STAT: signal transducer and activator of transcription, NF-κB: nuclear factor kappa B, NRP2: neuropilin-2, MCP-1: monocyte chemoattractant protein-1, VTE: venous thromboembolism, GI: gastrointestinal, TGF-β: transforming growth factor-beta, PDGF: platelet-derived growth factor, CTGF: connective tissue growth factor

current evidence remains incomplete, better characterization of macrophage subsets and their interaction with the tissue microenvironment may ultimately lead to more effective and less toxic therapies in sarcoidosis.[5,7,81]

CONCLUSION

Sarcoidosis is a multisystem granulomatous disease with complex and incompletely understood pathobiology involving genetic, environmental, epigenetic, and immunologic factors. In addition to its heterogeneous etiology, sarcoidosis demonstrates significant clinical variability in organ involvement, disease progression, and outcomes among affected individuals. As macrophages and T lymphocytes represent the principal cellular components of granulomatous inflammation, understanding their dynamic interplay is essential for clarifying disease mechanisms and improving therapeutic strategies. Emerging evidence indicates that macrophage polarization is not limited to the classical M1/M2 paradigm but rather represents a dynamic and reversible spectrum influenced by cytokine signaling, metabolic pathways, and the tissue microenvironment. Notably, drugs exert different and sometimes profound effects on this pattern and microenvironment. Although suppression of a single inflammatory pathway may control granulomatous inflammation, it may also result in immune dysfunction, increased susceptibility to infection, or progressive fibrosis. Recent advances in transcriptomics, single-cell technologies, and targeted immunotherapies have improved our understanding of macrophage heterogeneity and may provide opportunities for more precise and individualized therapeutic approaches. Nevertheless, the exact mechanisms underlying macrophage polarization and fibrotic progression in sarcoidosis remain incompletely defined; they require further validation in human studies and in advanced laboratory models, and a greater understanding of drug effects on these microenvironments.

Footnotes

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