Review

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Treat to target and tight control: Could be a new approach in the treatment of sarcoidosis?

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SUMMARY Sarcoidosis is a chronic granulomatous disease with multisystemic involvement. Although it is accepted as a benign disease, it can sometimes cause life-threatening organ (heart, brain) involvement that determines the prognosis of the disease. There are conflicting opinions about the treatment of the disease. In the generally accepted treatment approach the "step-by-step" model has gained weight. According to this approach, corticosteroids (CS) drugs alone are preferred in the first step in patients who require treatment. In the second step, immunosuppressive drugs (IS) are used in patients who do not respond to CS and/or have contraindications to CS use, and biologics (TNF-alpha inhibitors) are used in the third step. This treatment approach may be valid in cases with mild sarcoidosis. However, although sarcoidosis is considered a benign and self-limiting disease in some major organ involvement, the "step-by-step" approach may be a treatment option that puts the patient's life in danger. In such selected patients, much more rigorous, early and combined treatment approaches that definitely include CS, IS or biologic drugs may be required. In selected sarcoidosis patients with high risk, early diagnosis, "treat-to-target" (T2T) and "tight control" follow-up of patients seems to be a rational approach. This article reviews the "step-down" treatment regimens in light of recent literature data and hypothesizes that the T2T model may be a probable new treatment approach in patients with sarcoidosis.

Keywords sarcoidosis, treat-to-target, tight control, remission, new approach

1. Introduction

Sarcoidosis is a chronic multisystem inflammatory disease characterized by granuloma formation. Although the pathogenesis of the disease is not clear, it is thought to develop as a result of immune system dysregulation triggered by an unknown antigen in people with a genetic background (*1*). Sarcoidosis is a heterogeneous disease that may be asymptomatic or may present with different clinical presentations (*2*). It can often cause lung, eye, skin and musculoskeletal system involvement. It can also present with different life-threatening organ involvement, which is rare but determines the prognosis of the disease (*3*).

The diagnosis is made in the presence of non-caseating granulomas in histopathology, exclusion of other possible causes, and existence of clinical and radiologic findings supporting sarcoidosis (*4,5*). The treatment of the disease is mainly based on case series and retrospective uncontrolled studies, rather than multicenter controlled prospective studies (*6*). This brings with it different and complex views in the literature. When the diagnosis of sarcoidosis is made, it must first be decided whether the patient needs any treatment or just follow-up. In cases with sarcoidosis requiring treatment all organs involved with sarcoidosis should be detected before starting treatment (*7*). Therefore, all system and organ scans may be performed and as an imaging method, positron emission computed tomography (PET-CT) may be preferred. This method shows the extent of the disease, the correct determination of the biopsy site to be taken, and disease activation (*8*). PET-CT imaging may help to determine asymptomatic bone involvement as well to change the stage of the disease and the associated treatment decision. In rheumatology practice, early diagnosis and treatment, and more frequent patient follow-up strategies have opened a new era in the treatment of these patients (*9*). This model provides better remission rates, less organ involvement, less radiological progression and destructive disease, and higher quality of life, especially in patients with rheumatoid arthritis (RA) (*10*). We hypothesize that a

similar approach in patients with severe sarcoidosis may affect disease control, organ damage, quality of life and mortality.

2. General treatment approaches in sarcoidosis

The treatment of sarcoidosis is as still complex and controversial as its diagnosis (*11*). The main reason for this is that treatment strategies are usually based on case series and expert opinion rather than randomized-controlled studies. While discussing the treatment of sarcoidosis, the involvement of organs affected by the disease and the presentation of the disease (acute/chronic), as well as gender, age, race, and presence of comorbid disease should be considered (*12*). Sarcoidosis is a disease that regresses spontaneously and mostly does not require treatment. While spontaneous remission is common in patients with stage 1 and 2 sarcoidosis (between 55–90%), spontaneous regression is rare (10–20%) in stage 3 (*13*). Acute sarcoidosis cases have a better prognosis compared to chronic patients, often do not require treatment and spontaneous recovery is usually seen. However, chronic disease and/or recurrent cases should be treated (*14*).

While the "wait and see" approach seems reasonable in asymptomatic and mild cases, different treatment approaches may be required in high-risk patients who must be treated (*15*) (Table 1). According to the European Respiratory Society (ERS) protocols, "step-by-step" strategies are recommended for the treatment of sarcoidosis (*16*). Corticosteroids (CS) drugs are the first step of treatment (*17*). In addition to their anti-inflammatory and immunomodulatory effects, they have been shown to correct impaired Th1/Th2 cytokine dysbalance in patients with sarcoidosis (*18*). It was observed that CS treatment in pulmonary sarcoidosis caused significant improvement in radiological improvement and respiratory functions (*19*). In another study, patients with spontaneous remission were compared with patients going into remission with CS use , and it was shown that relapses were more common in patients using CS (*20*). In the presence of eye involvement, neurosarcoidosis, cardiac and renal sarcoidosis, chronic locomotor system involvement (muscle, bone, joints) and hypercalcemia, CS indication is available (*21*).

CS drug indications arise in severe skin involvement and the presence of constitutional symptoms such as fever, fatigue, and weakness (*22*). While it has been accepted that CS are the first choice of treatment, the confusion of drug dosage and duration of treatment still continues. Immunosuppressive (IS) drugs are used in second-line treatment of sarcoidosis (*23*). Various IS drugs such as methotrexate (MTX), azathioprine (AZA), and hydroxychloroquine (HQ) are use especially in CS-resistant patients or in cases where steroids are not preferred due to side effects (*24-26*). In the third step of treatment, biological drugs such as TNF-alpha inhibitors (TNFi), rituximab (RTX), and tocilizumab (TCZ) are preferred (*27,28*). The most experience is available

Table 1. Low *vs.* high risk sarcoidosis patients according to demographic, radiologic, laboratory and clinical phenotype

Features	Low risk	High risk
Gender	male	female
Age	young	elderly
Ethnicity	Caucasian	Afro-American
Clinical phenotype	Löfgren's syndrome	chronic sarcoidosis
Pulmonary	acute alveolitis, normal PFT/DLCO	bronchial obstruction, pulmonary fibrosis, pulmonary hypertension, low PFT/DLCO
Neurosarcoidosis	facial nerve palsy, aseptic menengitis, isolated headache, vertigo	intracranial mass, spinal cord, optic neuritis, epilepsy
Eye	anterior uveitis, conjunctivitis, lacrimal gland swelling, pseudotumor	panuveitis, retinal vasculitis, orbital myozit, optic neuritis
Heart	pericarditis, supraventricular arrhythmia, intracardiac mass, valvulopathy	A-V blocks, ventricular tachicardia myocarditis, aneurisma, cardiomyopathy
Skin	erythema nodosum, skar sarcoidosis, makülopapüler lezyonlar hipo/hiperpigmentasyon	lupus pernio, alopesi
Musculoskeletal	arthralgia, acute arthritis, tendinitis	chronic arthritis, Jaccoud, dactilitys, sarcoid myopathy, bone lesions
Kidney	hypercalcemia, hypercalciuria	nephrocalcinosis, renal failure
Radiographic stage	stage 1/2	stage 3/4
Laboratory findings	low CRP, low TNF-A, HLA-DQB1*0201	high sIL-2R, hypercalcemia, hypercalciuria, high TNF-A, HLA-DQB1*1501

PFT: pulmonary function tests; A-V: atrio-ventricular; sIL-2R: soluble interleukine-2 receptor; TNF-A: tumor necrosis factor-alpha; DLCO: diffusion lung carbonmonoxide; CRP: C-reactive protein; HLA: human leukocyte antigen.

using TNFi (*29*). The studies have shown that TNFi is an effective option in different organ involvement (pulmonary, neurosarcoidosis, eye, skin, heart, muscle, joint, kidney, liver) (*30*). It should be noted that randomized controlled studies on the efficacy and safety of these drugs in patients with sarcoidosis are limited in the literature. The available data are mostly based on open studies, case reports and expert experience.

3. Principles of "treat to target and tight control" strategies: when and which patients

In RA patients, early diagnosis and treatment ensures early remission of the disease and prevents chronic complications (*31*). This treatment and follow-up model introduced about a decade ago has resulted in better remission rates, less organ involvement, less radiological progression and destructive disease, and a higher quality of life (*32*). The most important point of this model is early diagnosis, determining the treatment target and choosing the appropriate disease modifying anti-rheumatic drugs (DMARDs) to reach this target and initiating early treatment (*33*). The target in the treatment of RA was determined as complete remission and/or low disease activity, and this target was achieved with more frequent outpatient follow-up of the patient (*34*).

The diagnosis and treatment principles, disease activation scores, and remission criteria are clearly defined in RA, while these are not clear yet in sarcoidosis. The treatment in RA is determined in line with the results of randomized-controlled studies and meta-analysis. However these studies in sarcoidosis are insufficient, therefore conflict and debate continues in treatment principles. In order for this successful model in RA to be applied to patients with sarcoidosis, a new perspective on sarcoidosis is required. The paradigm that sarcoidosis is a "benign and mild" disease should be changed, and diagnostic criteria, disease activation scores, organ involvement, radiological imaging priority and remission criteria should be redefined. The concept of early diagnosis and early treatment in selected severe sarcoidosis should be supported by further studies to support the hypothesis that it can prevent complications of the disease and organ damage and improve quality of life. With the early diagnosis of sarcoidosis, organ involvement and complications may be prevented. As in rheumatic diseases lung involvement, if sarcoidosis lung involvement is detected and treated at an early stage, the development of fibrosis may be prevented. However, chest radiography recommended for diagnosis and still used in the Scadding classification is insufficient for the early diagnosis of pulmonary sarcoidosis (*35,36*). Contrast-enhanced thoracic CT seems to be essential for early diagnosis in pulmonary sarcoidosis (*37*). However the activation and extent of the disease is very important. Patients diagnosed as stage 1 pulmonary sarcoidosis or only skin sarcoidosis may also have other "hidden site" involvement such as heart and bone. Therefore, after the diagnosis of sarcoidosis is made, organ and system screening may be performed and "high risk" patients may be determined. Although it seems to be an expensive method, PET-CT may be an alternative method in terms of early diagnosis, disease extent, long-term disease follow-up, early initiation of TNFi and response to treatment (*38*).

After the early diagnosis and organ involvement are determined, the patients who should definitely receive treatment should be identified and treatment should be started as soon as possible (Table 2). Patients with sarcoidosis who have started treatment should be followed up more frequently ("tight control") , follow-up parameters (acute phase reactant, pulmonary function tests, *etc.*), drug efficacy and side-effect profile should be evaluated at each visit.

4. Rationale for early, aggressive and "step-down" treatment in sarcoidosis: some evidence

Sarcoidosis is a difficult to treat disease because "everybody has a different opinion" when treatment comes to the fore. The difficulty of treatment is not due

Table 2. Selected severe sarcoidosis patients which should be treated in accordance with "step-down" (combined drugs) strategy

Involvement	Diseases
Heart involvement	A-V blocks ventricular arrythmia myocarditis aneurisma cardiomyopathy
Neurosarcoidosis	intracranial mass spinal cord epilepsy parenchimal lessions
Lung involvement	bronchial obstruction acute active alveolitis ("ground-glass") pulmonary hypertension low PFT/DLCO progressive lung disease extended parenchimal infiltrations
Eye involvement	panuveitis retinal vasculitis orbital myozit optic neuritis unresponsiveness to local treatment
Kidney involvement	symptomatic hypercalcemia hypercalciuria acute renal failure
Musculoskeletal system involvement	chronic arthritis bone lessions dactylitis sarcoid myopathy
Chronic skin disease	lupus pernio
Progressive symptomatic extrapulmonary disease Sarcoidosis-associated fatique Small-fiber neuropathy	

PFT: pulmonary function tests; A-V: atrio-ventricular; DLCO: diffusion lung carbon monoxide.

to the difficulty of the disease, but to the fact that the treatment principles have not been clearly determined yet (*39*). The decision about "which patients" to treat depends on two main factors: the risk of death or organ failure, and the deterioration of quality of life (*40-42*). Compared with the general population, sarcoidosis causes an increase in mortality (*43*). The most common causes of death from sarcoidosis are lung and heart diseases (*44*). In addition to pulmonary and cardiac disease, neurological involvement and multiorgan sarcoidosis are most closely associated with poor outcomes (*45*). Features such as pulmonary hypertension, decreased lung function, and pulmonary fibrosis have been shown to increase the risk of death from pulmonary disease (*46*). Irreversible organ damage to the brain, eyes or kidneys due to sarcoidosis can also cause significant morbidity (*47*). Sarcoidosis-related fatigue and small fiber neuropathy are important findings that reduce the quality of life of patients (*48,49*). When evaluating all of these together, it is understood that severe multisystemic sarcoidosis is not a "benign" disease, but in some situation may be a fatal and damaging disease (*50*). It is a fact that has to develop new treatment approaches in order to prevent mortality and morbidity and improve the quality of life of patients (Table 3).

According to ERS recommendations, "step-by-step" treatment models are recommended in sarcoidosis (*16*). CS is the first step treatment option recommended to be started alone in all organ involvement. The second step is recommended to start IS drugs when unresponsive to CS treatment and/or CS-related side effects develop. It is known that the effects of DMARDs which are frequently used in rheumatology practice start late (average 1-3 months) (*51*). Considering the recurrent rates in sarcoidosis and the late onset of DMARDs, it would be more rational to start DMARDs and CS

Table 3. Summary of sarcoidosis treatment strategies

Sarcoidosis phenotypes	ERS/ATS/WASOG (Step-by-step strategy) 1. Fırst-line 2. Second line 3. Third line 4. Fourth line	Step-down strategy (combined drugs use) 1. Fırst-line 2. Second line 3. Third line 4. Fourth line
Pulmonary Sarcoidosis		
Low risk	1. CS	1. CS
Intermediate risk	1. CS 2. IS(MTX,AZA,LEF) 3. IFX, ADA 4. RTX, JAKi, RCI	1. CS 2. IS(MTX,AZA,LEF) 3. IFX, ADA 4. RTX, JAKi, RCI
High risk	1. CS 2. IS 3. IFX, ADA 4. RTX, JAKi, RCI	1. CS+IS(MTX,AZA,LEF) 2. IFX, ADA 3. RTX, JAKi, RCI - After sustained remission achieved step-down discontinue drugs
Skin	1. Topical/systemic CS 2. IS (MTX, AZA, HQ) 3. IFX,ADA 4. Apremilast, JAKi	1. Topical/systemic CS 2. IS (MTX, AZA, HQ) 3. IFX, ADA 4. Apremilast, JAKi - Combined drugs use in lupus pernio - After sustained remission achieved step-down discontinue drugs
Heart	1. CS+/-IS 2. IS(MTX, AZA,LEF) 3. IFX, ADA 4. CyA	1. CS+IS(MTX, CyA) +/-IFX 2. IFX, ADA - After sustained remission achieved step-down discontinue drugs
Neurosarcoidosis	1. CS 2. IS(MTX, AZA, MM,HQ 3. IFX, ADA	1. CS+IS (MTX, AZA, MM, HQ) 2. IFX, ADA - After sustained remission achieved step-down discontinue drugs
Sarcoidosis-associated fatigue	1. Exercize 2. Armodafinil/D-metylphenidate 3. Low-dose CS and/or MTX	1. Exercize + HQ(MTX)+low-dose CS 2. Sympthomatic drugs-Armodafinil/D-metylphenidate - After sustained remission achieved step-down discontinue drugs
Musculoskeletal system (chronic arthritis, myositis, bone)	1. CS 2. IS(MTX, AZA, MM,HQ 3. IFX, ADA	1. CS+IS(MTX, AZA, MM,HQ 2. IFX, ADA, JAKi - After sustained remission achieved step-down discontinue drugs
Eyes	1. CS eye drops 2. CS 3. IS(MTX, AZA, MM,HQ 4. IFX, ADA	1. CS eye drops 2. CS 3. IS(MTX, AZA, MM,HQ) 4. IFX, ADA - Combined drugs use(CS + IS +/- IFX) in severe form(retinal vasculitis/ panuveitis, optic neuritis, acute loss of vision) - After sustained remission achieved step-down discontinue drugs

ERS: European Respiratory Society; WASOG: World Association of Sarcoidosis and Other Granulomatous diseases; ATS: American Thoracic Society; MTX: methotrexate; CS: corticosteroid; AZA: azathyoprine; MM: mycophenolat mofetil; RTX: rituximab; HQ: hydroxychloroquine; IS: immunosuppresive drugs; IFX: infliximab; ADA: adalimumab; CyA: cyclophosphamide; JAKi: janus kinase inhibitor; LEF: leflunomide; RCI: repository corticotropine inhibitor.

drugs simultaneously, especially in cases with severe sarcoidosis.

CS, as with RA should be considered a "bridging therapy" (*52*). Early initiation of DMARDs may also prevent disease relapses. This approach may also protect against the side effects (osteoporosis, diabetes, hirsutism, cataract, hypertension, *etc*.) that develop due to chronic use of CS (*53*). There are few studies in the literature showing and supporting the early onset of DMARDs in sarcoidosis. Nagai *et al.* showed that MTX and CS combination therapy gave better results for left ventricular function than CS alone in patients with cardiac sarcoidosis (*54*). Arun *et al.* showed that early IS treatments with AZA, MTX and infliximab (IFX) could effectively improve clinical outcomes in patients with neurosarcoidosis (*55*). The treatment records of 3276 sarcoidosis patients registered in the RISE (Rheumatology Informatics System for Effectiveness) system were examined. Most patients (59.3%) received CS, while only 18.2% of patients received CS monotherapy. While MTX and HQ were the most commonly used coventional DMARDs, 12.1% of patients received one or more biological or targeted synthetic DMARDs, with the most common being TNFi (*56*). A randomized controlled trial comparing the efficacy and tolerability of prednisone and MTX as first-line therapy in pulmonary sarcoidosis (PREDMETH study) is ongoing (*clinicaltrials.gov*) (*57*). The study aims to show that MTX is as effective as prednisone as a first-line treatment for sarcoidosis, but with fewer side effects. Gavrysyuk *et al.* compared the efficacy, tolerability, and recurrent rates of MTX and methylprednisolone (MP) in 143 newly diagnosed patients with pulmonary sarcoidosis (*58*). They showed that MTX monotherapy was not significantly different from MP monotherapy in terms of efficacy and rate of serious adverse events. However, they reported a significant reduction in the incidence of treatment resistance and relapse rate in patients receiving MTX. Goljan-Geremek *et al.* showed that MTX as monotherapy in the treatment of chronic pulmonary sarcoidosis is as safe and effective as steroids and patients experience definite pulmonary function tests (PFT) improvement (*59*). Ballul *et al.* compare the efficacy of CS alone or associated with IS drugs for the prevention of relapse in cardiac sarcoidosis (*60*). The authors showed that the combination of CS with IS drugs might reduce the risk of cardiac relapse, as compared to CS alone. Cardiac sarcoidosis multi-center randomized controlled trial (CHASM CS-RCT) is an ongoing study evaluating the optimal initial treatment strategy for patients with active cardiac sarcoidosis (*61*). The authors hypothesize that a low dose prednisone/MTX combination will have non-inferior efficacy compared to standard dose prednisone and that these combinations may result in significantly better quality of life and few side effects compared to standard dose prednisone. The same approach applies to biologic drugs. Biological drugs such as TNFi are often reserved for severe cases of refractory sarcoidosis, as outlined in the ERS guidelines and take months sometimes years to get started (*62*). These drugs are generally used in treatment-resistant severe sarcoidosis cases, and there is not enough data in the literature on its use in early disease treatment. In one study, it was shown that there is less chance of restoration of intrinsic conduction and cardiac function if delays in effective treatment for cardiac sarcoidosis (*63*). Baughman *et al.* compared the treatment outcomes of IFX and MTX in pulmonary sarcoidosis and found that IFX was more likely to improve clinical status than MTX (*64*). Sohn *et al.* showed that the use of TNFi in patients with neurosarcoidosis resulted in earlier disease control and better prognosis (*65*). In one study, the high disease activity detected with 18-FDG-PET-CT was associated with the effectiveness of TNFi (*66*). In other words, in the presence of active disease detected by PET-CT, especially in cardiac involvement, early biological initiation may increase the treatment success. Simonini *et al.* showed superior efficacy of adalimumab (ADA) in the treatment of childhood resistant chronic uveitis (including sarcoid uveitis) when used as a first line drug (*67*). According to a Delphi consensus study on sarcoidosis treatment it revealed large variations in treatment strategies but recommended the use of IS drugs in disease and required prolonged treatment or as a steroid-sparing agent in patients with high risk of steroid toxicity (*68*). However, the Delphi study does not provide firm guidance on exactly when to initiate DMARDs (first-line as monotherapy, combination with CS, or after failed CS treatment). As the above-mentioned studies increase, there will undoubtedly be more researchers supporting early and targeted therapy models for sarcoidosis.

5. Conclusions

The treatment of sarcoidosis is still controversial, and the debate about this treatment is as old as the disease itself. In most patients with a mild course, the "step-by-step" approach recommended by the ERS guidelines should be preferred. In selected patients with severe organ involvement (heart, lung, neurosarcoidosis), it is obvious that early, aggressive and combined treatment will reduce the risk of morbidity and mortality. It may be possible to achieve early disease remission, decrease organ damage and relapses and improve quality of life in sarcoidosis with treat-to-target and tight control strategy. Although ERS recommendations are open to discussion and criticism, their strength is based on existing studies. Multicenter randomized controlled studies are needed to change these treatment recommendations and to identify new treatment strategies.

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References

1. Newman LS, Rose CS, Maier LA. Sarcoidosis. N Engl J Med.1997; 336:1224-1234.
2. Chen ES, Moller DR. Etiology of sarcoidosis. Clin Chest Med. 2008; 29:365-377,vii.
3. Gupta SK, Chatterjee S, Roy M. Clinical profile of sarcoidosis in India. Lung India. 1982; 1:5-10.
4. Baughman RP, Lower EE, du Bois RM. Sarcoidosis. Lancet. 2003; 361:1111–1118.
5. Broos CE, van Nimwegen M, Hoogsteden HC, Hendriks RW, Kool M, van den Blink B. Granuloma formation in pulmonary sarcoidosis. Front Immunol. 2013; 4:437.
6. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med. 1999; 160:736-755.
7. James WE, Baughman R. Treatment of sarcoidosis: grading the evidence. Expert Rev Clin Pharmacol. 2018; 11:677-687.
8. Youn P, Francis RJ, Preston H, Lake F. Subcutaneous sarcoidosis (Darier-Roussy sarcoidosis) with extensive disease on positron emission tomography: A case report and review of the literature. Respirol Case Rep. 2022; 10:e0949.
9. Duarte C, Ferreira RJO, Santos EJF, da Silva JAP. Treating-to-target in rheumatology: Theory and practice. Best Pract Res Clin Rheumatol. 2022; 36:101735.
10. Singh JA. Treatment guidelines in rheumatoid arthritis. Rheum Dis Clin North Am. 2022; 48:679-689.
11. Gerke AK. Treatment of sarcoidosis: A multidisciplinary approach. Front Immunol. 2020; 11:545413.
12. Culver DA, Judson MA. New advances in the management of pulmonary sarcoidosis. BMJ. 2019; 367:l5553.
13. Innabi A, Alzghoul BN, Kalra S, Al-Hakim T, Buchanan M, Shivas T, Xue W, Gomez-Manjarres D, Patel DC. Sarcoidosis among US Hispanics in a nationwide registry. Respir Med. 2021; 190:106682.
14. Belperio JA, Shaikh F, Abtin FG, Fishbein MC, Weigt SS, Saggar R, Lynch JP 3rd. Diagnosis and Treatment of Pulmonary Sarcoidosis: A Review. JAMA. 2022; 327:856-867.
15. Perlman DM, Sudheendra MT, Furuya Y, Shenoy C, Kalra R, Roukoz H, Markowitz J, Maier LA, Bhargava M. Clinical presentation and treatment of high-risk sarcoidosis. Ann Am Thorac Soc. 2021; 18:1935-1947.
16. Baughman RP, Valeyre D, Korsten P, *et al.* ERS clinical practice guidelines on treatment of sarcoidosis. Eur Respir J. 2021; 58:2004079.
17. Judson MA. Corticosteroids in sarcoidosis. Rheum Dis Clin North Am. 2016; 42:119-135, ix.
18. Wilsher ML. Friend or foe? Corticosteroids in sarcoidosis. Respirology. 2022; 27:190-191.
19. Paramothayan NS, Jones PW. Corticosteroids for pulmonary sarcoidosis. Cochrane Database Syst Rev. 2000; (2):CD001114.
20. Sharma OP. Pulmonary sarcoidosis and corticosteroids. Am Rev Respir Dis. 1993; 147:1598-1600.
21. Winterbauer RH, Kirtland SH, Corley DE. Treatment with corticosteroids. Clin Chest Med. 1997; 18:843-851.
22. Judson MA, Chaudhry H, Louis A, Lee K, Yucel R. The effect of corticosteroids on quality of life in a sarcoidosis clinic: The results of a propensity analysis. Respir Med. 2015; 109:526-531.
23. Judson MA. Corticosteroid-sparing drugs in sarcoidosis: How should we assess them? Lung. 2021; 199:85-86.
24. Baughman RP. Methotrexate for sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 1998; 15:147-149.
25. El Jammal T, Jamilloux Y, Gerfaud-Valentin M, Valeyre D, Sève P. Refractory sarcoidosis: A review. Ther Clin Risk Manag. 2020; 16:323-345.
26. Brito-Zerón P, Pérez-Alvarez R, Pallarés L, Retamozo S, Baughman RP, Ramos-Casals M, SarcoGEAS-SEMI Study Group. Sarcoidosis: An update on current pharmacotherapy options and future directions. Expert Opin Pharmacother. 2016; 17:2431-2448.
27. Lower EE, Sturdivant M, Grate L, Baughman RP. Use of third-line therapies in advanced sarcoidosis. Clin Exp Rheumatol. 2020; 38:834-840.
28. Obi ON, Lower EE, Baughman RP. Biologic and advanced immunomodulating therapeutic options for sarcoidosis: A clinical update. Expert Rev Clin Pharmacol. 2021; 14:179-210.
29. Crommelin H, Vorselaars A, van der Vis J, Deneer V, van Moorsel CHM. Pharmacogenetics of anti-tumor necrosis factor therapy in severe sarcoidosis. Curr Opin Pulm Med. 2020; 26:267-276.
30. Adler BL, Wang CJ, Bui TL, Schilperoort HM, Armstrong AW. Anti-tumor necrosis factor agents in sarcoidosis: A systematic review of efficacy and safety. Semin Arthritis Rheum. 2019; 48:1093-1104.
31. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: A review. JAMA. 2018; 320:1360-1372.
32. Desai SP, Leatherwood C, Forman M, Ko E, Stevens E, Iversen M, Xu C, Lu B, Solomon DH. Treat-to-target approach in rheumatoid arthritis: A quality improvement trial. Arthritis Care Res (Hoboken). 2021; 73:207-214.
33. Smolen JS, Breedveld FC, Burmester GR, *et al.* Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis. 2016; 75:3-15.
34. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, Kincaid W, Porter D. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): A single-blind randomised controlled trial. Lancet. 2004; 364:263-269.
35. Culver DA, Baughman RP. It's time to evolve from Scadding: phenotyping sarcoidosis. Eur Respir J. 2018; 51:1800050.
36. Kobak S, Saydam G, Ince O, Sever F. Sensitivity of chest radiography in the early diagnosis of sarcoidosis: is it really should be done? Ann Rheum Dis. 2015; 74:859.
37. Nunes H, Brillet PY, Valeyre D, Brauner MW, Wells AU. Imaging in sarcoidosis. Semin Respir Crit Care Med. 2007; 28:102-120.
38. Akaike G, Itani M, Shah H, Ahuja J, Yilmaz Gunes B, Assaker R, Behnia F. PET/CT in the diagnosis and workup of sarcoidosis: focus on atypical manifestations. Radiographics. 2018; 38:1536-1549.
39. Selroos O. Treatment of sarcoidosis. Sarcoidosis. 1994; 11:80-83.

40. Crouser ED, Maier LA, Wilson KC, *et al.* Diagnosis and detection of sarcoidosis. An official American thoracic society clinical practice guideline. Am J Respir Crit Care Med. 2020; 201:e26-e51.
41. Baughman RP, Scholand MB, Rahaghi FF. Clinical phenotyping: Role in treatment decisions in sarcoidosis. Eur Respir Rev. 2020; 29:190145.
42. de Vries J, Lower EE, Drent M. Quality of life in sarcoidosis: Assessment and management. Semin Respir Crit Care Med. 2010; 31:485-493.
43. Kirkil G, Lower EE, Baughman RP. Predictors of mortality in pulmonary sarcoidosis. Chest. 2018; 153:105-113.
44. Swigris JJ, Olson AL, Huie TJ, Fernandez-Perez ER, Solomon J, Sprunger D, Brown KK. Sarcoidosis-related mortality in the United States from 1988 to 2007. Am J Respir Crit Care Med. 2011; 183:1524-1530.
45. Kobak S. Catch the rainbow: Prognostic factor of sarcoidosis. Lung India. 2020; 37:425-432.
46. Huitema MP, Mathijssen H, Mager JJ, Snijder RJ, Grutters JC, Post MC. Sarcoidosis-associated pulmonary hypertension. Semin Respir Crit Care Med. 2020; 41:659-672.
47. Gerke AK. Morbidity and mortality in sarcoidosis. Curr Opin Pulm Med. 2014; 20:472-478.
48. Atkins C, Wilson AM. Managing fatigue in sarcoidosis - A systematic review of the evidence. Chron Respir Dis. 2017; 14:161-173.
49. Tavee JO, Karwa K, Ahmed Z, Thompson N, Parambil J, Culver DA. Sarcoidosis-associated small fiber neuropathy in a large cohort: Clinical aspects and response to IVIG and anti-TNF alpha treatment. Respir Med. 2017; 126:135-138.
50. Baughman RP, Wells A. Advanced sarcoidosis. Curr Opin Pulm Med. 2019; 25:497-504.
51. Schett G, Emery P, Tanaka Y, Burmester G, Pisetsky DS, Naredo E, Fautrel B, van Vollenhoven R. Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: Current evidence and future directions. Ann Rheum Dis. 2016; 75:1428-1437.
52. Stacy JM, Greenmyer JR, Beal JR, Sahmoun AE, Diri E. The efficacy of low dose short-term prednisone therapy for remission induction in newly diagnosed rheumatoid arthritis patients. Adv Rheumatol. 2021; 61:50.
53. Kahlmann V, Moor CC, Veltkamp M, Wijsenbeek MS. Patient reported side-effects of prednisone and methotrexate in a real-world sarcoidosis population. Chron Respir Dis. 2021; 18:14799731211031935.
54. Nagai S, Yokomatsu T, Tanizawa K, Ikezoe K, Handa T, Ito Y, Ogino S, Izumi T. Treatment with methotrexate and low-dose corticosteroids in sarcoidosis patients with cardiac lesions. Intern Med. 2014; 53:427-433.
55. Arun T, Palace J. Effects of immunotherapies and clinical outcomes in neurosarcoidosis: A retrospective cohort study. J Neurol. 2021; 268:2466-2472.
56. Hammam N, Evans M, Morgan E, Reimold A, Anastasiou C, Kay JL, Yazdany J, Schmajuk G. Treatment of Sarcoidosis in US Rheumatology Practices: Data from the American College of Rheumatology's rheumatology informatics system for effectiveness (RISE) registry. Arthritis Care Res (Hoboken). 2022; 74:371-376.
57. Kahlmann V, Janssen Bonás M, Moor CC, van Moorsel CHM, Kool M, Kraaijvanger R, Grutters JC, Overgaauw M, Veltkamp M, Wijsenbeek MS; Collaborating investigators. Design of a randomized controlled trial to evaluate effectiveness of methotrexate versus prednisone as first-line treatment for pulmonary sarcoidosis: The PREDMETH study. BMC Pulm Med. 2020; 20:271.
58. Gavrysyuk V, Merenkova I, Dziublyk Y, Morska N, Pendalchuk N, Bychenko O, Vlasova N. Efficacy and tolerability of methotrexate and methylprednisolone in a comparative assessment of the primary and long-term outcomes in patients with pulmonary sarcoidosis. Diagnostics (Basel). 2021; 11:1289.
59. Goljan-Geremek A, Bednarek M, Franczuk M, *et al.* Methotrexate as a single agent for treating pulmonary sarcoidosis: a single centre real-life prospective study. Pneumonol Alergol Pol. 2014; 82(6):518-533.
60. Ballul T, Borie R, Crestani B, Daugas E, Descamps V, Dieude P, Dossier A, Extramiana F, van Gysel D, Papo T, Sacre K. Treatment of cardiac sarcoidosis: A comparative study of steroids and steroids plus immunosuppressive drugs. Int J Cardiol. 2019; 276:208-211.
61. Birnie D, Beanlands RSB, Nery P, *et al.* Cardiac sarcoidosis multicenter randomized controlled trial (CHASM CS- RCT). Am Heart J. 2020; 220:246-252.
62. Boleto G, Vieira M, Desbois AC, Saadoun D, Cacoub P. Emerging molecular targets for the treatment of refractory sarcoidosis. Front Med (Lausanne). 2020; 7:594133.
63. Kaida T, Inomata T, Minami Y, Yazaki M, Fujita T, Iida Y, Ikeda Y, Nabeta T, Ishii S, Naruke T, Maekawa E, Koitabashi T, Ako J. Importance of early diagnosis of cardiac sarcoidosis in patients with complete atrioventricular block. Int Heart J. 2018; 59:772-778.
64. Baughman RP, Drent M, Kavuru M, *et al*. Sarcoidosis investigators. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med. 2006; 174:795-802.
65. Sohn M, Culver DA, Judson MA, Scott TF, Tavee J, Nozaki K. Spinal cord neurosarcoidosis. Am J Med Sci. 2014; 347:195-198.
66. Vorselaars AD, Crommelin HA, Deneer VH, Meek B, Claessen AM, Keijsers RG, van Moorsel CH, Grutters JC. Effectiveness of infliximab in refractory FDG PET-positive sarcoidosis. Eur Respir J. 2015; 46:175-185.
67. Simonini G, Taddio A, Cattalini M, Caputo R, de Libero C, Parentin F, Pagnini I, Lepore L, Cimaz R. Superior efficacy of adalimumab in treating childhood refractory chronic uveitis when used as first biologic modifier drug: Adalimumab as starting anti-TNF-α therapy in childhood chronic uveitis. Pediatr Rheumatol Online J. 2013;11:16.
68. Rahaghi FF, Baughman RP, Saketkoo LA, *et al.* Delphi consensus recommendations for a treatment algorithm in pulmonary sarcoidosis. Eur Respir Rev. 2020; 29:190146.

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