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Update in treatment of pulmonary sarcoidosis

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Abstract:

Sarcoidosis is a chronic granulomatous multisystem disease with an unknown etiology. The diagnosis of sarcoidosis relies on the presence of noncaseating granuloma on histopathological examination with compatible clinical presentation and exclusion of other causes of granulomatous inflammation. Lungs and intrathoracic lymph nodes are the most commonly affected organs. Most of the patients are asymptomatic. Symptomatic patients generally have spontaneous resolution. 25% of patients have progressive lung disease and 10% of patients have organ failure. Corticosteroids, immunosuppressive, cytotoxic, and antimalarial drugs are used for sarcoidosis treatment. The decision of appropriate treatment is very important. The aim of this review is to summarize the actual treatment of pulmonary sarcoidosis.

Keywords:

Corticosteroids, immunosuppressive agents, pulmonary sarcoidosis, treatment

Introduction

Sarcoidosis is a chronic granulomatous multisystem disease with an unknown etiology. It develops in genetically susceptible individuals with environmental, occupational, or infectious exposure.[1,2]

Main pathological tissue infiltration is noncaseating granuloma. The diagnosis of sarcoidosis relies on the presence of noncaseating granuloma on histopathological examination with compatible clinical presentation and exclusion of other causes of granulomatous inflammation.[3,4]

Managing patients with sarcoidosis is sometimes difficult for clinicians because of heterogeneous manifestations and relatively lack of enough data on treatment. Corticosteroids, immunosuppressive, cytotoxic, and antimalarial drugs are used for sarcoidosis treatment. The decision of appropriate treatment is very important. The aim of this review is to summarize the treatment of pulmonary sarcoidosis.

Epidemiology

The incidence of sarcoidosis varies according to the ethnic groups. The highest incidence is observed among African-Americans (17–35 per 100,000 population) followed by Whites (5–12 per 100,000 population), while the lowest annual incidence is reported among Asians and Hispanics (1–3 per 100,000 population). Female-to-male prevalence ratio is 2:1. Sarcoidosis is a disease of middle-aged people, with the average age of 35–50 years.[5]

Clinical Manifestations of Pulmonary Sarcoidosis

Lungs and intrathoracic lymph nodes are the most commonly affected organs in sarcoidosis (over 90% of patients).[5-12] The clinical findings of pulmonary sarcoidosis are variable. It can change from asymptomatic

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condition to progressive life-threatening disease. Most of the patients are asymptomatic. In symptomatic patients, cough, dyspnea, or chest discomfort can be found. Symptomatic patients generally have spontaneous resolution. 25% of patients have progressive lung disease and 10% of patients have organ failure.[13-15]

Pulmonary sarcoidosis can be categorized into four stages according to the radiological features [Table 1]. The prognosis is less favorable with more advanced stages. Spontaneous regression is 80% in Stage I and chronic respiratory impairment is less than 5%. However, spontaneous regression of radiographic abnormalities is seen in only one-third of patients with Stage III disease, and chronic respiratory impairment is 5-fold increase in patients with Stage III and Stage IV diseases compared with Stage I disease.[16-19]

Diagnosis

Clinical and radiological findings are not enough for definitive diagnosis. Further, only presence of noncaseating granuloma on biopsy is not enough because of several other diseases that can cause similar histopathological changes. Compatible clinical, radiological, and histopathological findings with exclusion of other causes are needed for the definitive diagnosis. The only exceptions that we do not need histopathological diagnosis are:

1. Löfgren syndrome (bilateral hilar adenopathy, erythema nodosum, fever, and arthritis)
2. Heerfordt–Waldenström syndrome or uveoparotid fever (fever, parotid enlargement, facial palsy, and anterior uveitis)
3. Asymptomatic bilateral hilar lymphadenopathy.

In these situations, a careful follow-up must be done to confirm the diagnosis.[20,21] After the diagnosis of sarcoidosis, evaluation must be done for other comorbidities such as heart failure or pulmonary hypertension that can contribute to the symptoms but not respond to corticosteroid therapy.[22]

Table 1: Stages of pulmonary sarcoidosis

Stage	Radiographic features	Frequency (%)
I	Mediastinal and hilar lymphadenopathy (usually bilateral) without pulmonary infiltrates	40-50
II	Mediastinal and hilar lymphadenopathy (usually bilateral) with pulmonary infiltrates	30-40
III	Pulmonary infiltrates without lymphadenopathy (lymphadenopathy already regresses)	15-20
IV	Pulmonary fibrosis with volume loss. No lymphadenopathy	2-5

Treatment of Pulmonary Sarcoidosis with Corticosteroids

Most of the sarcoidosis patients have asymptomatic or nonprogressive diseases that regress spontaneously. In progressive symptomatic disease, there is not any permanent cure. Corticosteroids are the most preferred drugs in sarcoidosis treatment. They used for relief of the symptoms and control of respiratory impairment, but they do not cure the disease. They attenuate the granulomatous inflammation and prevent the development of irreversible end-organ damage such as fibrotic lung disease and honeycombing. When we could not use corticosteroids because of toxicity or patient-related contraindications, we can use other agents [Table 2]. Indications, optimal duration of treatment, avoiding excess toxicity from medications, and monitorization of the response to therapy are the main points.

First of all, we must decide to whom we should treat or observe. Sarcoidosis patients who do not need systemic therapy and can be followed are:

1. Asymptomatic patients with Stage I disease: Most of them (60–80%) have spontaneous remission
2. Asymptomatic patients with Stage II disease: In this group, patients have normal or mild obstructive or restrictive pulmonary function. We may give inhaled steroids to patients with obstructive pulmonary function test. However, before starting systemic corticosteroid therapy, we must observe them at least 3–6 months for progression of pulmonary function impairment or gas exchange. 50% of patients without progression will have spontaneous resolution by 36 months
3. Asymptomatic patients with Stage III disease: We may give inhaled steroids to patients with obstructive pulmonary function test, and we must follow them for 3–6 months. 33% of patients without progression may have spontaneous resolution.[23]
    - Effect of inhaled steroids in sarcoidosis is conflicting. They modulate the alveolitis in sarcoidosis. Improvement in cough, dyspnea, and wheezing is seen by using inhaled steroids, but no improvement is seen in pulmonary functions.[24] Inhaled steroids doses for sarcoidosis are budesonide (800–1600 mcg twice daily) and fluticasone (500–1000 mcg twice daily). These drugs are advised at least for 4–8 weeks. Indications of inhaled steroids are:[25]
        - Mild pulmonary symptoms (cough or dyspnea) or abnormal pulmonary functions in Stage I or II disease
        - Instead of long-term low-dose (5–10 mg daily) prednisone[24,25]

Table 2: Drugs used in pulmonary sarcoidosis treatment

Drugs	Indication	Dosage	Duration	Mechanism of action
Corticosteroids	Combinations of Severe pulmonary symptoms Abnormal or progressive pulmonary functions Diffuse or worsening radiographic changes	20-40 mg/day (oral prednisone or equivalents)	Initial therapy: 1-2 months It must be reduced 5-10 mg every 1-3 months until 10-15 mg/day. Maintenance therapy: At least 6-8 months The treatment period should be completed to 1 year	Attenuation of granulomatous inflammation and prevention the development of irreversible end-organ damage
Methotrexate	Corticosteroid intolerance Disease progression despite corticosteroid treatment Generally, used as steroid-sparing agent	Beginning dosage 5-7.5 mg/week. Then every 2 weeks, 2.5 mg/week is increased until 10-15 mg/week	Total 1 g drug dose or 18-24 months of therapy is related to hepatotoxicity	Anti-inflammatory, immunosuppressive and antimetabolite
Azathioprine	Methotrexate therapy failure Generally used with corticosteroids	Starting dose is 50 mg/day orally. The dose is increased by 25 mg every 2-3 weeks until the maintenance dose (2 mg/kg, maximum 200 mg/day)	There is not an exact duration time	Suppresses cellular immunity and inhibits lymphocyte proliferation via affecting DNA and RNA synthesis
Leflunomide	Generally used for extrapulmonary sarcoidosis; usage in pulmonary sarcoidosis is rare	20 mg/day	There is not an exact duration time	Antimetabolite
MMF	Steroid-sparing agent	1.5 or 3 g daily, in divided doses	There is not an exact duration time	Lymphocyte proliferation and activity inhibitor
Infliximab	Treatment failure in case of corticosteroid plus one of the second-line agents Generally, preferred in extrapulmonary sarcoidosis	3-5 mg/kg intravenous infusion	There is not an exact duration time	Monoclonal antibody which neutralizes TNF-α
Adalimumab	Treatment failure in case of corticosteroid plus one of the second line agents Effectiveness in pulmonary sarcoidosis is not certain	40 mg/week	There is not an exact duration time	Human anti-TNF antibody

TNF-α: Tumor necrosis factor alpha, MMF: Mycophenolate mofetil

During follow-up, if patients have the combination of these finding below, we should start systemic therapy:

- Severe pulmonary symptoms (dyspnea, cough, and chest tightness)
- Progressive pulmonary function abnormalities:
  - ≥4 decrease in oxygen saturation at rest or exercise or
  - ≥15% decrease in forced vital capacity (FVC) or
  - ≥10% decrease in total lung capacity (TLC) or
  - ≥20% decrease in diffusing lung capacity (DLCO).
- Worsening radiographic changes.[15,26,17]

In clinically severe disease, we should start systemic corticosteroid therapy without waiting. These patients generally have combination of:

- Severe pulmonary symptoms (dyspnea, cough, and chest tightness)
- Abnormal pulmonary functions:
  - FEV1 and FVC <70% and/or
  - DLCO <60% and/or
  - Oxygen saturation ≤90
- Diffuse radiographic opacities.[15,26,27]

Before starting corticosteroids, patients must be evaluated for latent tuberculosis and hepatitis B. If needed, prophylactic drugs must be started for them.

The initial sarcoidosis therapy dose for oral prednisone is 20–40 mg/day (0.3–0.6 mg/kg ideal body weight). If the clinical findings are not severe and the disease is slowly progressive, 20 mg/day oral prednisone will be appropriate. Otherwise, 40 mg/day oral prednisone must be preferred.[28]

Initial therapy must be continued for 4–8 weeks. Then, the patient must be controlled. If clinical and radiological findings and pulmonary function tests are improved, the dose will be reduced 5–10 mg every

4–12 weeks until 10–15 mg/day. Maintenance dose must be continued for at least 6–8 months. The treatment period should be completed to 1 year. If the parameters are not improved, the initial dose must be continued for additional 4–6 weeks. Then initial dose is reduced to maintenance dose and the treatment is completed to 1 year. When symptoms reappear, the dose can be increased 10–20 mg/day above the maintenance dose for 2–4 weeks.

In acute respiratory failure or nonpulmonary sarcoidosis (cardiac, neurologic, etc.), 80–100 mg/day (1 mg/kg/day) prednisone may be needed.

During follow-up, review of systems, physical examination, blood tests (complete blood count [cbc], creatinine, calcium, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), 25 hydroxyvitamin D, 1.25 hydroxyvitamin D), Electrocardiogram (EKG), and chest X-ray must be done every year. 24-h urine calcium must be evaluated at diagnosis and as indicated by symptoms. High-resolution computed tomography (HRCT), Magnetic resonance imaging (MRI), Holter, echocardiogram, and Thyroid-stimulating hormone (TSH) must be evaluated as indicated by symptoms. Bone density must be evaluated when corticosteroids started and then every 3 years.[16]

Serum angiotensin-converting enzyme (ACE) levels are elevated in 60% of sarcoidosis patients. Generally, sarcoidal granulomas produce ACE. However, serum ACE levels are not found useful in managing sarcoidosis. Furthermore, ACE inhibitor drugs suppress ACE levels.[16,22,27]

Relapses are frequent. Worsening of symptoms, radiological abnormalities, and pulmonary functions (10% decrease in FVC or TLC; decrease in PaO_2; increase in alveolar-arterial oxygen gradient) are indicators of relapse. In these patients, lifelong low-dose treatment (≤0.25 mg/kg/day or 0.25–0.5 mg/kg/alternate days) may be required.[28]

In follow-up, symptoms of the patient are the most important parameter. Further, improvement in radiological abnormalities and pulmonary functions (10% increase in FVC, TLC; 20% increase in DLCO; 4 mmHg increase in PaO_2; 4 mmHg decrease in alveolar-arterial oxygen gradient) is important to decide tapering prednisone dose. Hence, spirometry, DLCO, and oximetry must be done every 3–4 months follow-up and lung volumes must be measured every 12–24 months.[13]

Sometimes, symptoms may be discordant with radiological findings and pulmonary functions. In these patients, follow-up will help us. We must avoid early administration of corticosteroid therapy because it is related with relapsing disease.[13]

There are many adverse effects of systemic corticosteroid therapy. Weight gain, Cushingoid appearance, hirsutism, skin thinning, striae, posterior subcapsular cataract, exophthalmos, fluid retention, gastric irritation, steatohepatitis, increased risk of infections, hyperglycemia, psychiatric abnormalities, avascular necrosis, osteoporosis, myopathy, and leukocytosis are some of them. Before starting corticosteroid therapy, patient must be warned. The patient should be advised to pay attention to diet, salt, and sugar consumption.[16] For prevention of gastric irritation, proton pump inhibitors may be prescribed. Prevention of corticosteroid-induced osteoporosis is complex. Because sarcoid granulomas produce 1,25 hydroxyvitamin D. Further, calcium supplements may cause hypercalcemia and hypercalciuria. If there is not any hypercalcemia and hypercalciuria at the beginning of the treatment, 1200 mg/day calcium and 800 international unit/day Vitamin D intake is suggested. To prevent the risk of nephrolithiasis, dietary sources (milk, cheese, etc., of calcium must be preferred. Calcium and Vitamin D supplementation should be stopped when the corticosteroid therapy stopped. Bisphosphonates are recommended for prevention of bone loss for only patients with high fracture risk such as postmenopausal women or ≥50-year-old men who will use ≥7.5 mg/day prednisone for at least 3 months.[22,27]

Second-Line Agents

In some situations, corticosteroid therapy cannot be continued:

- Patient cannot tolerate the adverse effects of corticosteroids
- The disease progress and cannot be controlled despite moderate dose of corticosteroids (7.5–40 mg/day prednisone)
- Refusal of patient to take corticosteroids.

Agents used for the treatment of pulmonary sarcoidosis refractory to corticosteroid therapy are methotrexate, azathioprine, leflunomide, and mycophenolate. They may be used alone or with corticosteroids. At the end stage of pulmonary sarcoidosis, organ transplantation may be performed.[14]

Before changing corticosteroid therapy to second-line agents, patients should be asked whether they use medications regularly. Further, they must be evaluated for infections, pulmonary embolism, or pulmonary hypertension.[22,29,30]

End-stage lung fibrosis is one of the causes of corticosteroid unresponsiveness. If there is end-stage lung fibrosis, it is

also unresponsive to other immunosuppressive drugs. To distinguish whether there is active inflammation or not is difficult, because chest imaging and pulmonary function tests are not precise enough. Before lung transplantation, immunosuppressive therapy is generally tried.[31]

Methotrexate

Methotrexate is the most commonly used drug in the treatment of pulmonary sarcoidosis refractory to corticosteroid therapy. It is an anti-inflammatory, immunosuppressive, and antimetabolite drug. It can be used for pulmonary sarcoidosis patients and also skin, eye, and central nervous system involvement.[32] Clinical response rate of methotrexate for pulmonary sarcoidosis is 40%–60%.[22,33,34] Before using methotrexate, cbc, aminotransferases, alkaline phosphatase, bilirubin, creatinine, albumin, and hepatitis B and C viral testing must be evaluated. Patients with liver disease (aminotransferases level above two times the upper limit of normal or chronic hepatitis B or C infection) or renal disease (creatinine clearance <30 ml/min) cannot use methotrexate. Further, methotrexate is contraindicated in chronic alcohol users and pregnant women.

After initiation of the therapy, these blood tests other than viral panel must be assessed every 3–6 weeks until stable dose of the drug and then continued every 4–12 weeks. If aminotransferases increased without any cause, methotrexate dose must be tapered and then stopped. Hepatic toxicity may be occult. Hence, some authors suggest liver biopsy in these situations: (1) total dose of methotrexate achieved to 1 g; (2) 18–24 months of therapy; (3) 6 of 12 aminotransferases in a year are abnormal.[32,35]

Methotrexate has either oral or intramuscular forms. Generally, oral forms are preferred and 5–7.5 mg/week is the beginning dosage. Then, every 2 weeks, 2.5 mg/week is increased until 10–15 mg/week. If there is refractory nausea or unresponsive disease although 15 mg/week after 3–6 months of oral therapy, intramuscular form of the drug must be used.[32]

Methotrexate may be used alone or with corticosteroid therapy. By using low-dose methotrexate plus corticosteroid therapy, corticosteroid dose may be tapered with improvement of pulmonary functions. In patients who had methotrexate alone, adverse effects were seen in 30% of patients. Hence, combination therapy is generally preferred.[36,37] In the disease refractory to methotrexate, one of the other second-line drugs (azathioprine, leflunomide, or mycophenolate) may be combined with methotrexate.[33]

The most serious side effects of methotrexate are leukopenia, hepatic fibrosis, and interstitial pneumonitis. Hepatic fibrosis may be seen approximately in 10% of cases when the total dose exceeds 5 g. To distinguish hepatic toxicity from hepatic sarcoidosis, liver biopsy is needed.[22,38]

Methotrexate-induced interstitial pneumonitis is another adverse effect which is difficult to distinguish from progressive sarcoidosis-related interstitial lung disease. Ground-glass opacities, centrilobular nodules, and increased reticular opacities are typical in methotrexate-induced pneumonitis. Rarely, pleural effusions may be seen. These changes recover after stopping the drug. Blood eosinophilia is another finding that is more likely seen in methotrexate-induced interstitial pneumonitis than progression of sarcoidosis.[39-41]

Other adverse effects of methotrexate are teratogenicity, suppression of gonadal functions, nausea, alopecia, skin rash, and lymphoproliferative disorders. Some of the patients with lymphoproliferative disorder may regress after stopping methotrexate.[42,43]

Folic acid (1 mg/day or 5 mg/weekly) is routinely given to patients on chronic methotrexate therapy to reduce myelosuppression risk. Cbc must be evaluated every 1–2 months.[40]

Azathioprine

Azathioprine suppresses cellular immunity and inhibits lymphocyte proliferation via affecting DNA and RNA synthesis. It is used in patients with methotrexate therapy failure. The mechanism of azathioprine in sarcoidosis treatment is not clear. Azathioprine is generally used with corticosteroids.[44,45] Improvements in patients are similar in azathioprine and methotrexate groups, except for a high infection rate with azathioprine.[36]

Before initiating azathioprine, cbc, aminotransferases, creatinine, and serum albumin must be evaluated. Further, thiopurine-S-methyltransferase (TPMT) genotyping and/or serum TPMT enzyme activity levels generally may be assessed. Because azathioprine toxicity is related to its metabolites and TPMT is the enzyme that converts azathioprine to its metabolites.[46]

Azathioprine's starting dose is 50 mg/day orally. The dose is increased by 25 mg every 2–3 weeks until the maintenance dose (2 mg/kg, maximum 200 mg/day). Then, white blood cell count (WBC) must be monitored every week during dose escalation and every 8–12 weeks in stable period. If WBC falls to 4000/mm^3, azathioprine dose must be reduced. Further, serum aminotransferases must be evaluated every 8–12 weeks in the first several months, and then, less frequents checks are needed. After 3–6 months, prominent response to therapy can be raised.

Side effects of azathioprine are gastrointestinal complaints (nausea, vomiting, and diarrhea), fever, rash, malaise, and hematologic problems (suppression of all blood cell lines). Gastrointestinal side effects may be reduced by taking the drug with meal. Hematologic problems may be difficult to discriminate from suppression of bone marrow related to sarcoidosis. Other side effects are increase in aminotransferases and risk of malignancy.[31]

Leflunomide

Leflunomide is an antimetabolite drug. Generally, used for extrapulmonary sarcoidosis, the usage in pulmonary sarcoidosis is rare.[47-49] Before initiating leflunomide, cbc, aminotransferases, creatinine, serum albumin, and hepatitis B and C must be evaluated. Patients with aminotransferases level above two times the upper limit of normal or chronic hepatitis infection cannot use leflunomide. Alcohol avoidance and reliable contraception method are recommended during leflunomide therapy.[31]

Initiation dose of leflunomide is 20 mg/day. Alternatively, it can be 10 mg/day and can be increased to 20 mg/day. After 6–12 weeks, improvement in lung function occurs.[47]

Serum albumin and liver function tests must be monitored every 2–4 weeks for the first 3 months, followed by monitoring every 8–12 weeks for the next 3 months and every 12 weeks thereafter.[35]

Nausea, diarrhea, rash, peripheral neuropathy, abdominal pain, and hepatotoxicity are the most common side effects.[33,50]

Mycophenolate mofetil

Mycophenolate mofetil is a lymphocyte proliferation and activity inhibitor used in rheumatic disease-related interstitial lung diseases. Usage in sarcoidosis is limited. It can be used as a steroid-sparing agent. Nausea, diarrhea, and neutropenia are the most common side effects.[51,52]

Other drugs

Tumor necrosis factor alpha antagonists

In pulmonary sarcoidosis refractory to corticosteroids and one of the second-line agents, we can use tumor necrosis factor alpha (TNF-α) antagonists. TNF-α is related to inflammation and maintenance of granuloma in sarcoidosis.[53,54]

Infliximab, adalimumab, and etanercept are the TNF antagonists assessed in pulmonary sarcoidosis. Before initiating one of them, patient must be evaluated for latent infections including tuberculosis and hepatitis B and C. Hence, tuberculin skin test or peripheral blood interferon release assay for latent tuberculosis; as well as HbsAg, anti-HBc, and anti-HCV tests for hepatitis must be evaluated.[55,56]

Infliximab is a monoclonal antibody which neutralizes TNF-α. It was evaluated in pulmonary and extrapulmonary sarcoidosis.[57,58] Administration dose is 3–5 mg/kg intravenous infusion at 0, 2, 6, and 12 weeks. The optimal frequency and duration of infliximab in pulmonary sarcoidosis are unknown. Especially extrapulmonary sarcoidosis, patients receive more benefit than pulmonary sarcoidosis in long-term therapy.[56-59] Sarcoidosis patients with peripheral blood CD4+ T-cell lymphopenia who are resistance to immunosuppressant may be more likely to respond infliximab.[60]

Adalimumab is a human anti-TNF antibody. In some case series, improvement in extrapulmonary sarcoidosis was described. However, effectiveness in pulmonary sarcoidosis is not certain.[61] It is administered by subcutaneously. Optimal dose in sarcoidosis is unknown; however, in some case series, it was used as 40 mg/every week.[62]

Etanercept is a soluble TNF-α receptor fusion protein which binds TNF-α. It was assessed in a clinical trial of stage 2–3 pulmonary sarcoidosis patients. However, because of treatment failure, the trial was stopped.[63]

TNF-α antagonists can be combined with corticosteroids, methotrexate, or azathioprine in some diseases such as Crohn disease or rheumatoid arthritis. However, data in sarcoidosis are insufficient.

Off-label investigational drugs

Cyclophosphamide, rituximab, golimumab, ustekinumab, chloroquine, hydroxychloroquine, and antimycobacterial therapy (rifampin, ethambutol, levofloxacin, and azithromycin) were tried in sarcoidosis but are not commonly used due to side effects or inadequate data.[31]

Lung Transplantation

Lung transplantation may be promising to Stage IV sarcoidosis patients who have advanced pulmonary fibrosis and pulmonary hypertension. Timing of transplantation is not certain, but FVC less than 1.5 L (or <50% of predicted) and respiratory failure or pulmonary hypertension related to sarcoidosis are the features that predict transplantation requirement. Bilateral lung transplantation is more preferred than single-lung transplantation.[64] In patients with

cardiac involvement, heart and lung transplantation must be done.[65] Recurrence of sarcoidosis after lung transplantation is very rare and generally disappears in 3 months.[66,67]

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