CHAPTER 48

Current Concepts and Controversies in the Treatment of Pulmonary Sarcoidosis

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Sarcoidosis is a multisystem inflammatory disease of unknown etiology characterized histopathologically by noncaseating granulomas. Sarcoidosis may involve any organ, but the most frequently affected sites are the lungs, lymph nodes, skin, eyes, and liver. Usually at presentation most of the patients with pulmonary sarcoidosis are asymptomatic. When symptomatic, dyspnea, cough, or nonspecific chest discomfort are the common presentations. Spontaneous resolution of the disease is common, but progressive lung disease occurs in approximately 25 percent and disabling organ failure in up to 10 percent.

ORAL GLUCOCORTICOID THERAPY

Corticosteroids have long been the most commonly used agents for the treatment of pulmonary sarcoidosis. Most patients with pulmonary sarcoidosis do not require treatment, as a large chunk of patients have an asymptomatic, nonprogressive disease or experience spontaneous remission. For those with more severe pulmonary involvement, therapy is aimed at reducing the burden of inflammation and preventing the development of irreversible end-organ damage while avoiding excess toxicity from medications.

Prior to initiating corticosteroid therapy, patients should be assessed for comorbid diseases like infection, heart failure, thromboembolic disease, pulmonary hypertension.

MECHANISM OF ACTION OF GLUCOCORTICOIDS

Glucocorticoids appear to exert their effects on sarcoid granulomas through transcriptional regulation of glucocorticoid-receptor target genes and also non-genomic signal transduction pathways in lymphocytes and alveolar macrophages.

The usual indication for therapy of pulmonary sarcoidosis include

- Troublesome respiratory symptoms
- Worsening lung function, as assessed by successive pulmonary function testing at three to six month intervals, that demonstrates one or more of the following: a fall in total lung capacity (TLC) ≥ 10%; a fall in forced vital capacity (FVC) of ≥ 15%; a decrease in diffusing capacity (DLCO) of ≥ 20%; or worsened gas exchange at rest
- Progression radiographic changes including: worsening of opacities, development of cavities, progression of fibrosis or development of signs of pulmonary hypertension.

Therapy is not indicated in

- Asymptomatic patients with Stage I radiographic changes as approximately 60 to 80% of patients will have a spontaneous remission.
- Asymptomatic patients with Stage II radiographic changes and normal or mildly abnormal lung function as approximately 50 % of untreated patients will have radiographic resolution by 36 months.

DOSAGE AND ADMINISTRATION

Initial therapy

The optimal dose of glucocorticoids in sarcoidosis is not known, choosing a dose requires balancing the likelihood of response against the risk of adverse effects. Therapy is usually initiated with oral prednisone at a daily dose of 0.3 to 0.6 mg/kg ideal body weight (usually 20 to 40 mg/day), depending on the severity of disease activity. The initial dose is usually continued for four to six weeks and the patients are re-assessed, clinically; radio graphically and with pulmonary function tests for stability or improvement. If the patient is stable or has improved the dose of steroids is tapered (by 5 to 10 mg decrements every four to eight weeks) down to 0.2 to 0.4 mg/kg (usually 10 to 20 mg/day). If these parameters are unimproved, continue the initial dose for another four to six weeks.

High-dose oral glucocorticoid therapy (80 to 100 mg/day) may be warranted rarely in patients with acute respiratory failure or concomitant cardiac, neurologic, ocular, or upper airway disease.

Maintenance therapy

Recurrence of symptoms is common (occurring in about 60 percent of patients), so a continuation of the maintenance dose for at least six to eight months prevents it. A maintenance dose of prednisone in the range of 0.25 to 0.5 mg/kg (usually 10 to 20 mg) per day will prevent worsening of disease. During the maintenance phase, the patient is reassessed at four to twelve week intervals for evidence of symptomatic worsening or development of glucocorticoid-related adverse effects.

Assessing the response

A favorable response to glucocorticoid therapy is defined by:

- Improvement in symptoms

- A decrease in or clearance of radiographic abnormalities.
- Physiologic improvement, including a ≥ 10 to 15% improvement in FVC or TLC, a ≥ 20% improvement in DLCO, or an increase in gas exchange.

A failure to respond to therapy (or a relapse) is often defined as:

- A drop of 10 percent or more in FVC or TLC
- Worsening of radiographic opacities, especially with development of cavities, honeycombing, or signs of pulmonary hypertension
- Reduction in gas exchange at rest or with exercise

Duration of therapy

The appropriate duration of therapy in patients who respond to therapy is not known.

Treatment must be given for at least three to six months to be effective and to prevent relapse. Relapses are common following reduction or withdrawal of therapy. Lifelong low dose therapy (≤0.25 mg/kg per day) may be required in minority of the patients who suffer frequent relapses.

Treatment of Relapses

If there is relapse of the disease after tapering of the prednisone, the dose is increased to the last effective dose and continued for a subsequent three to six months. If there is no improvement after three months, prednisone is increased back to the initial effective dose (20 to 40 mg daily) until there is improvement (usually three to six months).

Failure of therapy

The patients who are unable to tolerate the adverse effects of glucocorticoids or whose disease cannot be controlled on the equivalent of prednisone 10 to 15 mg or less, or who have evidence of disease progression despite a moderate dose of prednisone, an alternative immunosuppressive agent may be of benefit. A variety of immunosuppressive agents have been used to treat refractory pulmonary sarcoidosis. The evidence in support of individual second-line agents is largely observational. The agents that appear to have the greatest likelihood of benefit with an acceptable side effect profile are methotrexate, azathioprine, and antimalarial agents. All of the alternative agents for patients with refractory pulmonary sarcoidosis carry substantial risk for toxicity, particularly myelosuppression, hepatotoxicity, and opportunistic infection. A trial of at least six months should last to allow adequate assessment of effectiveness.

METHOTREXATE

Methotrexate (MTX) is the most commonly used nonglucocorticoid immunosuppressive agent for sarcoidosis affecting the lungs, skin, eyes, and central nervous system.

Patients with evidence of underlying liver disease or chronic infection with hepatitis B or C are not candidates for MTX therapy. MTX is contraindicated in pregnancy and those with creatinine clearance < 30 mL/min.

Dosage and administration

The usual initiating dose is with oral therapy at a dose of 7.5 mg weekly. The dose is gradually increased (eg, by increments of 2.5 mg every two weeks) until a dose of 10 to 15 mg per week is achieved. Switch to intramuscular MTX if the patients have refractory nausea or have not achieved a beneficial effect after three to six months of oral therapy at 15 mg per week.

Adverse effects

The most serious side effects of immunosuppressive MTX therapy are hepatic fibrosis (in up to 10 percent of cases when the dose exceeds 5 g), leukopenia, and interstitial pneumonitis, resulting in pulmonary fibrosis. Other toxicities include nausea, alopecia, and skin rash.

AZATHIOPRINE

Azathioprine affects synthesis of RNA and DNA, thus inhibiting lymphocyte proliferation. Azathioprine is used as second line therapy for pulmonary sarcoidosis, generally as a supplement to glucocorticoids.

Dosage and administration

The usual starting dose of azathioprine is 50 mg per day, given as a single daily oral dose.

The dose is slowly increased by 25 mg every two to three weeks to reduce the likelihood of gastrointestinal side effects. The typical maintenance dose is 2 mg/kg (up to a maximum of 200 mg/day). Monitor the white blood cell count and reduce the azathioprine dose if the count falls to 4000/mm.

Adverse effects

Gastrointestinal complaints (eg, nausea, vomiting, and diarrhea), mild transaminitis, rash, fever, and malaise are the most common side effects. Hematologic side effects include depression of all cell lines. Azathioprine is a teratogenic.

Antimalarial agents

Chloroquine and hydroxychloroquine have immunomodulating properties. Clinical experience with chloroquine for pulmonary sarcoidosis is limited, and its relative efficacy versus other therapies has not been assessed. Due to the limited benefit and substantial toxicity, these drugs are avoided except in circumstances where other options have failed or are contraindicated.

Dosage and administration

For patients with a normal G6PD level, the dose of chloroquine is approximately 250 mg/day (maximum daily dose ≤2.3 mg/kg real body weight).

Adverse effects

The major adverse effect of chloroquine is irreversible retinopathy and blindness.

Tumor necrosis factor antagonists

Tumor necrosis factor alpha (TNFa) is thought to

accelerate the inflammatory process in sarcoidosis via its role in maintenance of granuloma formation. Due to the potential toxicity of these agents, they are reserved for patients who have persistent disease despite treatment with glucocorticoids (eg, prednisone ≥15 mg/day) and at least one second-line immunosuppressive agent (eg, methotrexate, azathioprine, leflunomide) . Various tumor necrosis factor antagonists studies in sarcoidosis include Infliximab, Adalimumab and Etanercept. Studies of the efficacy of TNFa antagonist agents in the treatment of sarcoidosis have yielded mixed results. Therapy with TNFa antagonists has been associated with reactivation of a variety of latent infections including tuberculosis and hepatitis B.

Experimental Drugs

Several medications proposed for pulmonary sarcoidosis are still considered experimental (eg, endothelin receptor antagonists, and pentoxifylline) or are used infrequently due to their side effect profile (eg, cyclophosphamide). The role of mycophenolate in the treatment of pulmonary sarcoidosis requires further study.

Drugs to be avoided

Several medications proposed for use in pulmonary sarcoidosis are now avoided due to the lack of adequate supportive data or an adverse effect profile; these agents include colchicine, chlorambucil, cyclosporine, nonsteroidal anti-inflammatory agents, tetracyclines, and thalidomide.

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