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Original article

Thalidomide for improving cutaneous and pulmonary sarcoidosis in patients resistant or with contraindications to corticosteroids

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ABSTRACT

Background: Limited data report thalidomide improves cutaneous sarcoidosis; no benefit has been reported for pulmonary localization.
Objectives: To evaluate feasibility and efficacy of prolonged treatment with thalidomide for cutaneous sarcoidosis associated to pulmonary involvement in patients with resistance or contraindications to steroids.
Methods: Nineteen patients were treated with thalidomide for 24 months starting with 200 mg/d for first 2 weeks, followed by 100 mg/d for 11 weeks and a maintenance dose of 100 mg on alternate days for 35 weeks, and a gradual scaling down until therapy interruption. Criteria of efficacy were: skin score, serum ACE levels (s-ACE), chest X-ray (CXR), lung function tests (LFTs), and diffusing lung capacity for CO (DLCO). The skin score was computed as arithmetic sum of seven score parameters (min: 0, max: 28).
Results: Skin score significantly decreased ($P < 0.001$). Lower skin scores occurred after 3 and 6 months ($P < 0.05$). s-ACE levels decreased over time at the third month ($P < 0.001$). CXR assessed by radiological stage significantly improved during the first 6 months ($P < 0.001$). DLCO showed a continuous trend of improvement. Minor side effects that have forced the suspension of the drug were drowsiness/sedation (74%), constipation (68%), and weight gain (53%). Deep vein thrombosis of the lower limbs occurred in one patient (who did not drop out the study). Eight patients (42%) abandoned thalidomide for axonal sensitive peripheral neuropathy (PN) between the ninth and the 24th month of treatment.
Conclusions: Thalidomide, long-term at mid-low doses, can be considered as an effective therapeutic alternative in chronic sarcoidosis with resistance or contraindications to steroids.

1. Introduction

Sarcoidosis is a multisystem disease with an unknown etiology, which more frequently affects the skin, the lymph nodes, and the lungs. Diagnosis is based on a compatible clinical presentation, supported by histological evidence of noncaseating granulomas, with exclusion of other granulomatous diseases [1]. Sarcoidosis is associated with a T-helper cell type 1 immune response that expresses many proinflammatory cytokines and chemokines. Granuloma formation in sarcoidosis is mediated by increased secretion of interferon-gamma, interleukin-2, and tumor necrosis factor-alpha (TNF-α) [1,2]. Corticosteroids, although their long-term benefit is disputed, are the mainstay of treatment for sarcoidosis even if there is no consensus about when to start treatment, the dose of steroids and how long [3,4].

Immunosuppressive and cytotoxic agents can be used in addition to corticosteroids or as steroid-sparing agents to treat chronic refractory sarcoidosis [4–6] (Table 1). No studies have clearly defined when these agents should be used for treatment. Moreover, the high toxicity profile of these agents, including a neoplastic potential, has limited their use.

Inhibition of TNF with monoclonal antibodies has therefore received attention as an alternative in therapy-resistant sarcoidosis [7,8] (Table 1). The TNF antagonists compared to the conventional agents appear relatively safe, however caution is warranted because of the increased incidence of tuberculosis, which represents a diagnostic challenge in patients with sarcoidosis.

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Table 1
Drug therapy for sarcoidosis.

Drug	Specific indications	Adverse effects	Dose regimen	Comments
Sistemic corticosteroids	Acute or chronic systemic sarcoidosis	Associated with significant morbidity (Cushing's syndrome, fatigue, cataracts, glaucoma, weight gain, osteoporosis, opportunistic infections, diabetes, arterial hypertension, etc.)	0.5–1 mg/kg/d/PO or IM of prednisone or equivalent for 6–12 wk followed by a gradual dose reduction every 6–12 wk for at least 12 mo	Are still the mainstay of treatment; dose and duration of therapy often must be individualized
Inhaled corticosteroids (budesonide)	Pulmonary sarcoidosis most of all when associated with bronchial hyperresponsiveness	Few adverse effects respect to the systemic therapy	800 g three or two times daily in addition to corticosteroids PO for 6 mo and then alone for long-term maintenance treatment	Used as steroid-sparing agent; effective on respiratory symptoms and on disease relapse reduction
Methotrexate	Chronic systemic sarcoidosis	Haematological, gastrointestinal, pulmonary and hepatic cumulative risk of toxicity	7.5–30 mg/wk/PO or IM; the dosage is adjusted on the basis of white blood cells	Second-line treatment; can be used alone or as steroid-sparing agent
Leflunomide	Pulmonary and extrapulmonary chronic sarcoidosis	Similar to methotrexate however has less severe toxicity	10–20 mg/d/PO	Used as monotherapy or as add-on therapy (MTX) in progressive disease
Pentoxifylline	Pulmonary chronic sarcoidosis	Gastrointestinal adverse effects	25 mg/kg/d/PO (200–400 mg up to three times daily)	Used as monotherapy or as steroid-sparing agent
Antimalarians (chloroquine, hydroxychloroquine)	Pulmonary, cutaneous chronic sarcoidosis, and hypercalcaemia	Retina toxicity; gastrointestinal adverse effects; hydroxychloroquine is preferred because its lower risk of ocular toxicity	3.5–4 mg/Kg/d/PO of chloroquine or 6–6.5 mg/kg/d of hydroxychoroquine	Used as monotherapy or in combination of corticosteroids
Cyclophosphamide	Refractory neurosarcoidosis; miocardial refractory sarcoidosis	Hematologic and bladder toxicity; opportunistic infections; neoplastic potential	50–150 mg/d/PO or 500–2000 mg IV infused every 2 wks	Used as steroid-sparing agent
Azathioprine	Pulmonary chronic refractory sarcoidosis	Gastrointestinal symptoms; leucopenia; opportunistic infections	100–150 mg daily PO for at least 6 mo or until 2 yrs	Second-line treatment; can be used alone or as steroid-sparing agent in long-term treatment
Infliximab	Neurosarcoidosis; ocular, cutaneous, renal, and pulmonary refractory sarcoidosis	Increased risk of infections, local erytema	3–5 mg mg/kg/IV infused at weeks 0, 2, 6,12, 24 and followed through wk 52	Potential second-line therapy for ocular and neurosarcoidosis, can be used alone or as add-on therapy (MTX)
Etanercept	Ocular, cutaneous refractory sarcoidosis	Increased risk of tuberculosis reactivation	25–50 mg by SC injection/twice weekly or once weekly	As monotherapy or as steroid-sparing agent
Adalimumab	Cutaneous, pleural and pulmonary refractory sarcoidosis	Neoplastic potential	40 mg by SC injection every 2 wks	Used as monotherapy or as add-on therapy
Cyclosporine A	Skin, uveitis, refractory neurosarcoidosis	Increased risk of infections, renal disfunction, headache, hirsutism, gastrointestinal symptoms	5 mg/kg/day or greater	As monotherapy or as steroid-sparing agent

d: day; wk: week; mo: month; PO: orally; IM: intramuscular; IV: intravenous; SC: subcutaneous injection.