Effects of Pentoxifylline and Methylprednisolone Combined Therapy on Sarcoidosis

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Abstract

Sarcoidosis is a multisystem granulomatous disorder. Alveolar cells, in the course of sarcoidosis, produce TNF-α which is thought to play a pivotal role in granuloma formation. For patients with steroid complications, contraindications or resistance other alternative drugs have been evaluated. One of them is pentoxifylline (POF), which is shown to inhibit TNF-α production.

This report is about the results of combined therapy of methylprednisolone and POF in 4 sarcoidosis patients. Three of them improved significantly after 6 months' therapy. All had radiological regression. Serum angiotensin converting enzyme levels decreased from (U/L) 52, 128, 55 to 45, 52, and 23 respectively. Diffusing capacity of the lung for carbon monoxide (DLCO) increased from (% predicted) 49, 81, 52 to 58, 85, 80 respectively. 67 Gallium uptake suppressed in all three responder patients.

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Key words: *Sarcoidosis, Pentoxifylline, Methylprednisolone*

Introduction

Sarcoidosis is a multisystem disorder of unknown aetiology, occurs world wide, affecting all races, both sexes and all ages. Despite a number of investigations, the cause of sarcoidosis remains obscure. It is not known if either a single agent or multiple factors cause sarcoidosis (1,2). It is characterized in the affected organs by T-lymphocyte infiltration and granuloma formation. The lung is the most commonly involved organ (1,3,4).

A number of cytokines chemotactic for monocytes is produced by alveolar cells in the course of inflammatory reactions of sarcoidosis. The activated state of involved cells has been demonstrated by their spontaneous *ex vivo* cytokine production. TNF-α is one of the cytokines that has been identified in the course of sarcoidosis (2,5). It is thought to play a pivotal role in regulatory aspects of granuloma formation and sustenance (6,7,8). TNF-α, which is released by alveolar macrophages, is found in patients with progressing disease (2). Various cytokine production and in particular TNF-α release by alveolar macrophages is a crucial feature of the immunopathogenesis of sarcoidosis.

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The optimal treatment of patients with pulmonary sarcoidosis is not known. There is general agreement on the effect of corticosteroids but their effects on the overall natural history and any long time benefits are less certain (9). Because of the side effects associated with the long-term corticosteroid therapy and existence of some patients with sarcoidosis showing short-term or no response to corticosteroids, other alternative treatments have been proposed (1,6).

Besides the use of some cytotoxic agents there are now studies on anticytokine strategies. Pentoxifylline (POF); oxpentifylline, 3,7-dimethlyl-1-(5-oxohexyl)-xanthine is one of them which is used widely in the treatment of patients with various types of vascular insufficiency. Recently, POF has been shown to suppress the synthesis of TNF-α and interleukin-12 (IL-12) and can be used in the treatment of sarcoidosis (1,6,10,11,12,13).

In the light of this information, we used a treatment protocol: combination of POF (12,5 mg/kg twice a day orally) (6) and corticosteroid (40 mg daily oral methyl prednisolone, the dose was tapered by 8mg every 2 weeks to a maintenance dose of 4mg on alternate days), in four of our sarcoidosis patients who had a mono-corticosteroid therapy before (with the mentioned dose) with a recent deterioration of clinical symptoms and laboratory findings.

Case Presentations

Case 1

A 39-year old woman who was a non-smoker had a clinicoradiographic diagnosis of stage 1 sarcoidosis 3 years ago. The activity markers were negative except serum angiotensin converting enzyme (sACE) level of 197 u/L (normal: 8-52), so the patient was observed with 3 month intervals.

Because of a progressive splenomegalia she had undergone a splenectomy 2 years after the diagnosis; while her sACE level was 260 u/L. The pathology of the splenectomy material revealed the diagnosis of sarcoidosis. Because of this splenic involvement, corticosteroid monotherapy was started with the mentioned protocol. In the 4th month of the treatment, papular skin lesions occurred, pathologic diagnosis was sarcoidosis. She was considered as steroid resistant and the steroid therapy was combined with oral POF by the mentioned protocol.

The combined therapy was continued for 6 months. Neither radiological improvement nor a change in sACE level was observed. Meanwhile, skin lesions progressed. The therapy was ceased.
After two months skin lesions regressed spontaneously. She is now stable without having had treatment for 6 months.

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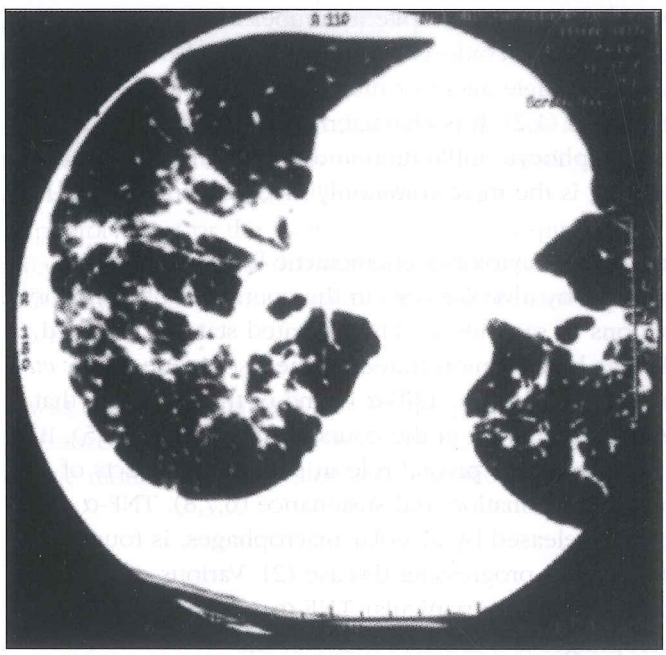

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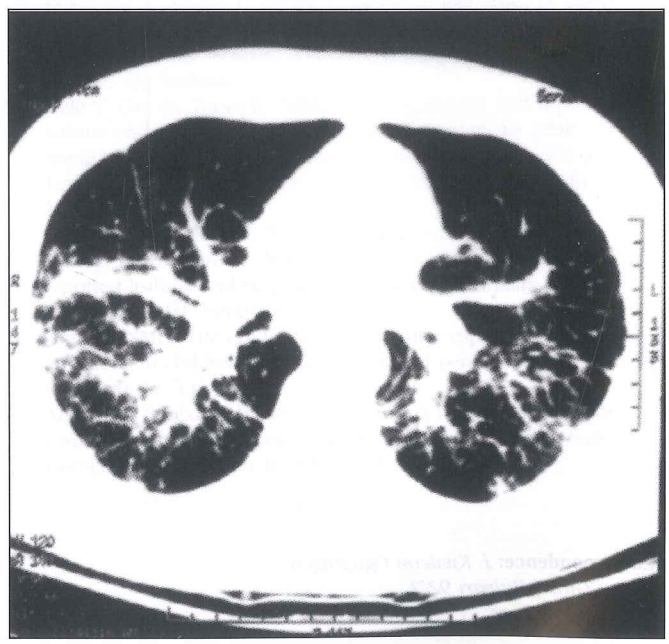
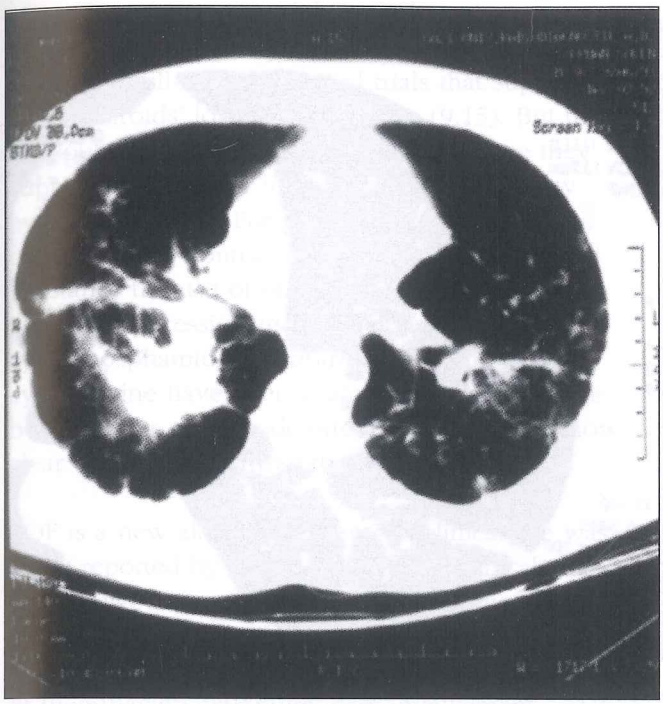


Figure 1. *Computed tomography of thorax done before (A) and after (B) methylprednisolone treatment.*

A



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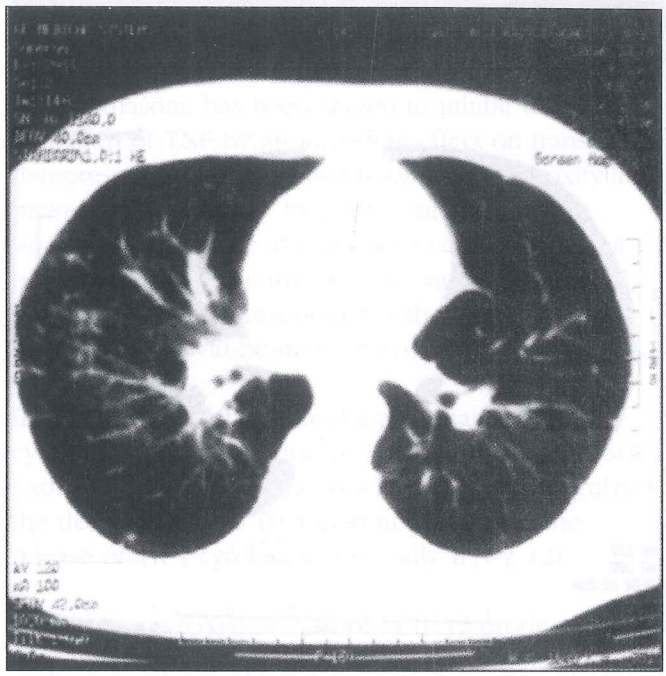

Figure 2. *Computed tomography of thorax done before (A) and 6 months after (B) combined POF therapy showing significant improvement.*

Case 2

A 33-year old man who did not smoke was admitted to our hospital for his malaise, which continued for 3 months after he had had pneumonia. He had bilaterally pulmonary infiltrates on the chest radiogram. He was investigated for sarcoidosis. He had a sACE level of 72 u/L; DLCO %58 and his chest-computed tomography showed multiple mediastinal lymph nodes, bilateral small pulmonary nodules and ground glass opacities. His bronchoscopy and biopsies revealed no pathognomonic signs. So he underwent an open lung biopsy. His pathological diagnosis was sarcoidosis. He was then started on a monotherapy of oral corticosteroid with the mentioned protocol for one year. He had a slight radiological regression (Figure 1) but no improvement in DLCO and sACE. The therapy was stopped.

One year after he was symptomatic of dyspnea, his radiology revealed progression, DLCO was 49% and sACE 52 u/L. He had a positive mediastinal and pulmonary 67-gallium uptake. He was started on the combined therapy with methylprednisolone and POF protocol. In the 3rd month of the therapy there was a significant radiological improvement. The improvement was better in the 6th month (Figure 2). DLCO improved to 58%. sACE level was 45 u/L. 67-gallium uptake was significantly suppressed. The therapy was continued for 9 months and then he himself discontinued the therapy. 3 months after stopping the therapy, clinical and radiological relapse reoccurred. The combined therapy protocol is planned again after a complete laboratory evaluation.

Case 3

A 26 year old non-smoking woman had had a sarcoidosis skin lesion. She was sent to our hospital because of a paratracheal mass on her chest radiogram. In her chest-computed tomography, she had multiple conglomerated mediastinal lymph nodes and bilateral small pulmonary nodules and thickened interlobular septae. Her bronchial biopsy specimen was reported as sarcoidosis. She had two phalangial lytic lesions on a conventional x-ray in her right hand and right foot. Bo~e biopsy was reported as sarcoidosis. Erythema and swelling were the clinical findings of these bone involvements. She had a sACE level of 16 u/L, DLCO 92%. On her 67 gallium scintigraphy, besides an intrathoracic uptake, she had extrathorasic accumulation of 67 gallium in salivary and lacrymal glands, bilateral inguinal lymphnodes, bilateral knees, right hand 4th –5th distal metacarpals, bilateral ankles, right foot 2nd digit.

Because of a symptomatic bone involvement and active alveolitis image on the chest tomography she

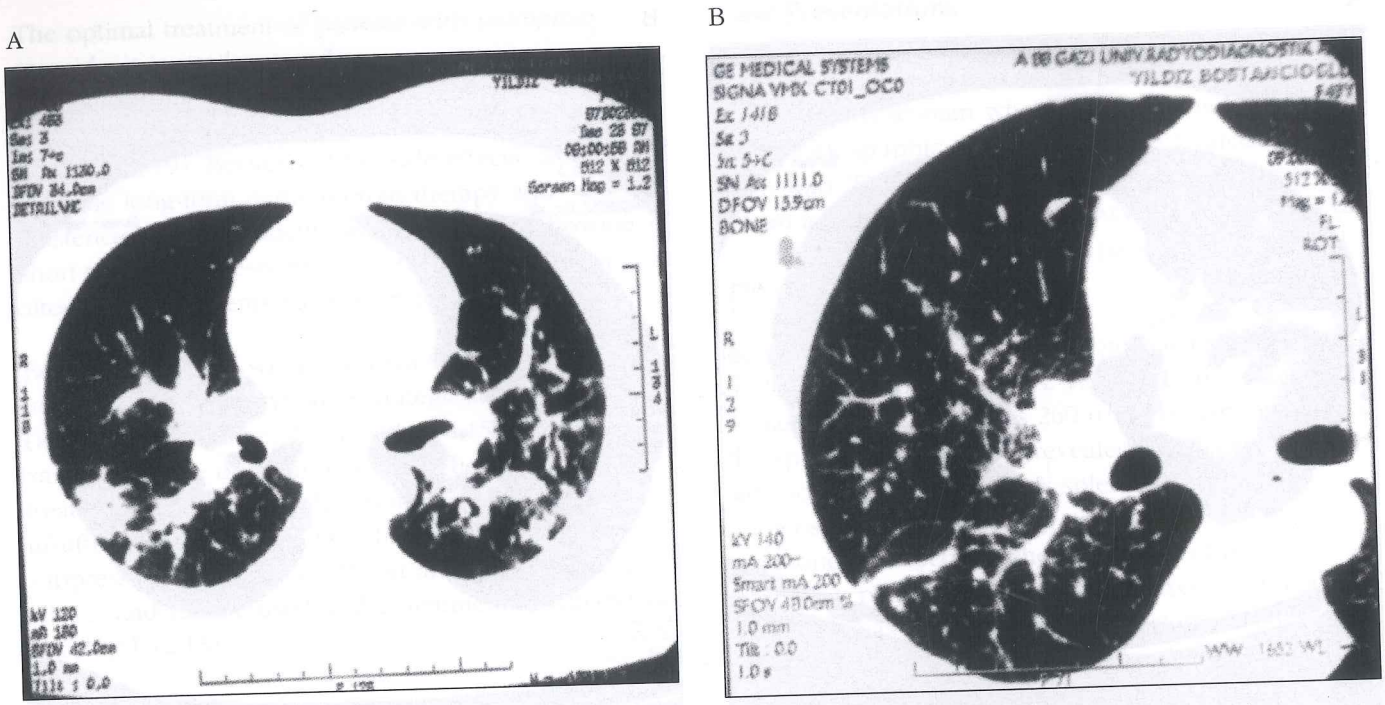

Figure 3. *Computed tomography of thorax showing significant regression of paranchimal lesions after 6 months' combined therapy (A. Before therapy, B. After therapy).*

was started on a steroid monotherapy with the mentioned protocol. She received this therapy for 6 months and she had a slight radiological regression but no improvement in skin and bone lesions. After a 3 month interval she had radiological progression, sACE level of 128 u/L, DLCO 81%. Skin lesions and finger hyperaemia and swelling progressed. She then was started on the combined protocol of methylprednisolone and POF.

After 8 months of therapy, radiological regression occurred, skin lesions regressed nearly totally. Finger hyperaemia and swelling disappeared. Her sACE level was 52 u/L, DLCO 85%. 67-gallium uptake was suppressed totally. It is now 12 months and she is still receiving the therapy.

Case 4

A 42 year old woman who had a mild persistent asthma for five years was investigated for her anemia. The chest X-Ray revealed an interstitial pattern. She had a sACE level of 5 u/L, DLCO %52. On her chest tomography she had multiple mediastinal lymphnodes, bilaterally diffuse reticulonodular opacities and patchy infiltration with thickened interlobular septae. Her bronchial biopsies were not pathognomonic. She was accepted as stage 2 sarcoidosis. She was started on a steroid mono-therapy. She had a minimal radiological improvement in the 7th month. At the end of one year she had no clinical or radiological improvement. The therapy was ceased.

After an 8 month interval she had clinical and radiological progression. She was symptomatic of dyspnea, and skin lesions occurred. Biopsy of these lesions revealed sarcoidosis. She had a positive parenchyma and mediastinal 67-gallium uptake, sACE level of 55 u/L and DLCO 40%. Then she started the mentioned combined therapy of methlyprednisolone and POF. She had a significant regression in her skin lesions in the 3rd month of the treatment. In the 6th month, a dramatic regression was seen in her chest tomography (Figure 3), there was a suppression of 67-gallium uptake, sACE level was 45 u/L, DLCO 57%. The therapy is now in the 12th month; the regression still goes on with a sACE level of 23 u/L and DLCO 80%.

Discussion

Because of the uncertain clinical course of sarcoidosis and its potential for spontaneous remissions the need for treatment must be assessed carefully. There are few guidelines regarding the indications of treatment (2,3,14). Symptomatic or progressive disease, life-threatening organ involvement is generally accepted to be an indication for a course of systemic therapy.

Oral corticosteroids are the first line treatment agents. However, some patients show a short-time response to corticosteroid therapy and some are resistant. There are still too few clinical trials that support corticosteroids' long-term outcome (9,15). But there is no doubt about their beneficial effect, since they suppress the cellular immune and inflammatory events (2,3,14,16). For patients with steroid complications, contra-indications or corticosteroid-resistance the use of other alternative drugs; immunosuppressive agents such as cyclophosphamide, methotrexate, azathioprine or cyclosporine have been evaluated (1,2,16,17). But besides their severe side effects, few patients show clear benefits from these therapeutic agents.

POF is a new alternative agent; its clinical use was firstly reported by Zabel et al. In that clinical study they showed a remarkable decrease of disease activity by using POF (6). We used this agent in combination with methlyprednisolone in four sarcoidosis patients, 3 of them having extrapulmonary involvement.

It has been shown that alveolar macrophages isolated from patients with sarcoidosis spontaneously release discrete amounts of TNF-α. In the lung, TNF-α appears to play a critical role in acute pulmonary injury and in the regulation of fibroblast growth. Furthermore, TNF-α acts as a neutrophil and monocyte chemotactic factor; it behaves as a stimulator and regulator of the synthesis and release of other lymphokines and increased prostaglandin production (18,19).

TNF-α inhibitory effect of POF has been shown in many invivo and invitro studies (2,10,11,12,13). Marques et al have shown the inhibition of exaggerated spontaneous TNF-α production from alveolar macrophages by POF in sarcoidosis patients (12). In a study of Han et al POF has been shown to strongly inhibit the accumulation of TNF mRNA in the TNF biosynthesis (10). In the same study, dexamethasone has been shown to inhibit the induction of TNF by an impeding effect on translation derepression. Since dexamethasone and pentoxifylline prevent TNF synthesis by exercising inhibition at separable points, the authors have concluded that it is not suprising to note that the two agents block TNF synthesis more effectively then either alone; so their combined use will be more effective (10).

IL-12, a product of activated macrophages is a key cytokine for the induction of Th 1 cells in sarcoidosis pathogenesis. The increased level of IL-12 upregulates the development of Th 1 cells and amplifies the release of Th 1 cytokines, especially IFN-γ (2).

Thus, pharmacological control of IL-12 production may be a key strategy in modulating specific immun-mediated diseases dominated by type-1 cytokine responses. Moller et al in their study have shown that POF suppressed IL 12 production *in vitro* at concentrations lower than those required to suppress TNF-α production, it is speculated that the same therapeutic concentrations of POF that inhibit TNF-α production *in vivo*, also suppress IL 12 production invivo. POF was also found to enhance the IL 12 suppressive effects of low doses of corticosteroids. This drug may have particular therapeutic utility when used in combination with low-dose corticosteroid therapy (13).

In our patients combined POF and corticosteroid therapy resulted in a significant clinically and laboratory improvement in three of our four sarcoidosis patients (Table 1).

Table 1. Demographics and laboratory values of patients

	Age (yr)	Stage of the disease	DLCO* (%)	DLCO** (%)	sACE* (U/L)	sACE** (U/L)	Therapy time (months)
Case 1	39	I	73	75	70	75	6
Case 2	33	II	49	58	52	45	9
Case 3	26	I	81	85	128	52	8
Case 4	42	II	40	80	55	23	12

*Before combined POF and corticosteroid therapy
**After combined POF and corticosteroid therapy

In case 1, the only activity marker was serum ACE level after splenectomy. Her skin lesions occurred under the corticosteroid treatment, so she was assessed as corticosteroid resistant. But she didn't reveal any clinical or radiological improvement under combined therapy. She than regressed spontaneously after the cessation of the therapy. The spontaneous resolution rate is mentioned as 60-80% in stage 1, 50%-60% in stage 2 in the literature (1,3).

In cases 2,3 and 4, combination therapy with POF revealed a significant regression of disease activity. These were confirmed by radiological imaging, DLCO, serum ACE levels and 67-gallium scans. These results provide evidence that POF can be considered as an effective treatment of active sarcoidosis in combination with steroid therapy since no such significant improvement was achieved in monosteroid therapy in any of these patients.

An interesting finding is the response of the extrapulmonary sarcoidosis to this combination therapy. Especially in case 3, the clinical signs of bone involvement have improved totally which is confirmed by total suppression of 67-gallium scan after therapy, though the cystic lesions persevered on the conventional x-ray as a sequel lesion.

As Zabel et al, we also cannot entirely exclude the possibility that some of the responses were due to spontaneous remission of the disease. But it will be unlikely to assess the achievement of such dramatic improvements as spontaneous remission, as the patients couldn't achieve a comparable improvement during their monotherapy with corticosteroids.

In our patients, combination therapy of corticosteroid and POF seems to be more effective than steroid therapy alone. POF was well tolerated. We didn't see any clinical or laboratory side effects of the therapy. As there were no side effects and as the patients achieved a significant improvement, their compliance to the therapy was excellent.

One point that must be determined is the duration of the therapy. We are planning to continue the treatment with a single agent: POF; after 12 months' combination therapy. In case 2, the relapse of the disease after ceasing the therapy support this idea.

In conclusion, these results suggest that combined POF and methylprednisolone therapy is promising. Further clinical trials are needed to determine its value in the treatment of sarcoidosis.

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