

Anti-fungal medication and sarcoidosis

Antimikotiki in sarkoidoza

Marjeta Terčelj,¹ Barbara Salobir,¹ Ragnar Rylander²

¹ Clinical Department of Pulmonary Diseases and Allergy, University Medical Centre, Ljubljana, Slovenia, e-mail: marjeta.tercelj@kclj.si, barbara.salobir.pulmo@kclj.si

² BioFact Environmental Health Research Center, Lerum, Sweden, e-mail envhealth@biofact.se

Korespondenca/ Correspondence:

Marjeta Terčelj, Clinical Department of Pulmonary Diseases and Allergy, University Medical Centre, Ljubljana, Slovenia, e-mail: marjeta.tercelj@kclj.si, barbara.salobir.pulmo@kclj.si
Tel.: +386 1 522 23 42

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Abstract

Background: Previous studies on sarcoidosis have shown that the addition of an anti-fungal medication to the traditional treatment with corticosteroids improves treatment efficiency. It cannot be excluded that the effect is due to a stimulatory effect of the anti-fungal medication on the action of corticosteroids. To assess this possibility a study was undertaken where patients with sarcoidosis stage 2 were given an anti-fungal medication only.

Material and methods: Study subjects (n=10) were recruited from newly diagnosed cases of sarcoidosis and observed for 3 months to reduce the risk of including patients with spontaneous regression of the disease. They were given an anti-fungal medication for 2–11 months and x-rays were taken before and every second month after starting the treatment. Diffusion capacity, serum angiotensin converting enzyme, and chitotriosidase were determined as markers of sarcoidosis activity.

Results: There were improvements in the x-ray findings as well as the markers of sarcoidosis in 8 out of 10 patients. Two patients had an exacerbation of their disease after two months and they were given corticosteroids in addition to the anti-fungal medication.

Comments: The results demonstrate that the beneficial effects of anti-fungal medication are specific and not caused by an improvement of corticosteroid efficacy. The findings provide a basis for larger clinical studies.

Izvleček

Izhodišča: Dosedanje študije o zdravljenju sarkoidoze so pokazale, da dodatek antimikotikov k rutinskemu zdravljenju s kortikosteroidi izboljša rezultate zdravljenja. Ali učinek antimikotikov vpliva na boljšo učinkovitost kortikosteroidov, ni bilo mogoče ugotoviti. Da bi ocenili morebitni vpliv antimikotikov, smo bolnikom s pljučno sarkoidozo v stadiju 2 dali samo antimikotike.

Material in metode: V študijo smo vključili 10 bolnikov z novo odkrito pljučno sarkoidozo in jih 3 mesece opazovali zaradi morebitnega spontanega umika bolezni. Nato smo jim 2–11 mesecev dajali antimikotike in opravili rentgensko slikanje pred uvedbo zdravljenja in po pričetku zdravljenja na dva meseca. Ravno tako smo pri vseh bolnikih opredelili difuzijsko kapaciteto pljuč, serumsko vrednost angiotenzin konvertaze (ACE) in hitotriozidazo (CTO) kot označevalce aktivnosti sarkoidoze.

Rezultati: Umik sprememb na rentgenskih slikah pljuč smo zaznali pri 8 od 10 bolnikov. Pri dveh bolnikih je bolezen blago napredovala po 2 mesecih zdravljenja in sta zato dobila še kortikosteroide ob nadaljevanju zdravljenja z antimikotiki.

Komentar: Vzorec bolnikov v študiji je majhen, zato jo bo potrebno ponoviti. Rezultati pa kažejo, da učinek antimikotikov ni povezan z izboljšanjem učinka kortikosteroidov, kar bo osnova večjih kliničnih raziskav.

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1. Introduction

In previous clinical observations it was unexpectedly found that pulmonary sarcoidosis improved after treating fungal sequelae with an anti-fungal medication. These observations prompted intervention studies and the first of these 18 patients with chronic sarcoidosis, unsuccessfully treated with corticosteroids, were given an anti-fungal medication in addition to corticosteroids. Significant improvements were found in 15 patients.¹ In a following study 50 patients with newly diagnosed pulmonary sarcoidosis were observed for 3 months or longer without treatment to avoid inclusion of subjects with early regression of the disease.² After this period they were randomly allotted into two groups, one receiving conventional corticosteroid treatment for 6 months and the other receiving corticosteroid + anti-fungal medication (itraconazole 200 mg daily) for 6 months. The X-ray scores and other markers of sarcoidosis decreased in both treatment groups. The X-ray scores and the levels of sarcoidosis markers decreased more after the treatment with anti-fungal medication as compared to corticosteroids only. Previous reports on the effect of anti-fungal treatment of sarcoidosis also include a small study where four subjects showed improvement after adding an anti-fungal medication to the corticosteroid treatment.³

Table 1: Duration of treatment (months) and X-ray scores before and after treatment with anti-fungal medication

Patient	duration	before	after	change
1	7	2	1	-1
2	6	2	1	-1
3	4	2	1	-1
4	9	3	0	-3
5	8	2	0	-2
6	6	1	0	-1
7	11	2	1	-1
8	4	2	1	-1
9	2	3	3	0
10	2	2	3	1

The beneficial effects of anti-fungal medication described above suggest that the fungal antigen is removed and that this diminishes the late hypersensitivity reaction.⁴ It cannot be ruled out, however, that the effect of anti-fungal medication is through increasing the efficiency of the corticosteroid treatment. The interaction between corticosteroids and anti-fungal drugs has been studied previously and it has been shown that this combination markedly enhanced suppression of endogenous cortisol secretion.⁵

In view of this, the following hypothesis was formulated: An anti-fungal medication improves the efficiency of corticosteroids. To test the hypothesis, a study was undertaken where patients with sarcoidosis were given an anti-fungal medication only.

2. Material and methods

Study patients were recruited from the Clinical Department of Respiratory Diseases and Allergy at the University Medical Centre Ljubljana, Slovenia. The department was conducting a study where an anti-fungal medication was given in addition to the traditional treatment with corticosteroids.² During the course of this study occasional patients refused corticosteroid treatment because of suspected side effects but they accepted anti-fungal medication. Such patients were included in the present study. The diagnosis was based on standard criteria⁶ and the presence of non-caseating granulomas was verified histologically. All lavages were cultured and some biopsies were stained to exclude the presence of fungal infection. Only one patient had IgG antibodies against *Aspergillus* and *Candida*.

The patients were given an anti-fungal medication (itraconazole 200 mg daily). This drug was chosen based on previous experience.² Before treatment and at every second month up to 11 months X-ray was performed with severity grading of granulomas according to a numerical score (0–4), judging size and extension of the infiltrates.² The scoring was made by an experienced radiologist without knowledge of the patient characteristics or treatment.

Table 2: Distribution of x-ray scores before and after treatment with anti-fungal medication

x-ray score	normal	1	2	3
before	0	1	7	2
after	2	6	0	2

In addition to the determination of x-ray scores, markers of sarcoidosis including diffusion capacity (DL_{CO}), serum angiotensin converting enzyme (sACE) and chitotriosidase (CTO) were determined using the earlier described techniques.²

The original study was approved by the Ethical committee of the University and informed consent was obtained from the participants.

3. Results

The results of the x-ray examinations are shown in Table 1.

It is seen that 8 out of 10 patients had improved x-ray findings after the treatment. In two patients there was no improvement or deterioration at 2 months. They were thus given corticosteroid treatment in addition.

Table 2 presents the number of patients with different x-ray scores before and after treatment.

If the number of patients with scores normal or 1 were compared before and after

treatment, there was a statistically significant difference ($p = 0.006$, Fisher's exact test).

Table 3 presents different indicators of sarcoidosis before and after treatment.

Overall diffusion capacity increased and different indicators of sarcoidosis decreased after treatment except in two patients with a 2 months' treatment period.

4. Comments

The major result of the study is that treatment with an anti-fungal medication without the addition of corticosteroids resulted in an improvement in different parameters of sarcoidosis in the majority of the patients. This was of the same magnitude as has previously been shown when an anti-fungal medication was given together with corticosteroids.^{1,2} The hypothesis that the effect of anti-fungal medication was due to an increase in corticosteroid treatment efficacy could thus be rejected.

The study has some shortcomings. The material is scarce and all patients knew they were taking anti-fungal medication. It cannot be excluded that some of the cases that improved represent those who would have had spontaneous regression of the disease anyway. On the other hand, it is highly unlikely that the knowledge of medication would have influenced pulmonary infiltrates and the patients were selected to avoid early regression of the disease. Furthermore, the possibility of spontaneous regression was also present in the earlier studies comparing treatment with corticosteroid + antifungal medications. Spontaneous regression would thus not influence the conclusion and the rejection of the hypothesis tested.

Two of the patients showed no evidence of improvement after two-month treatment and corticosteroid treatment had to be added, whereafter they improved. This suggests that in these patients the disease was caused by another agent. Another explanation could be in an insufficient absorption of the medication, which we could not test as no blood levels were determined.

Anti-fungal medication is well known to have side effects in some patients. Among our patients four reported muscular cramps,

Table 3: Markers of sarcoidosis before and after treatment with anti-fungal medication

Patient	DL _{CO}		sACE		CTO	
	before	after	before	after	before	after
1	98	97	0.47	0.17	627	576
2	94	102	0.55	0.45	13	15
3	77	84	0.35	0.13	243	135
4	81	88	0.60	0.19	363	29
5	87	92	0.11	0.11	2	2
6	95	102	0.53	0.39	45	59
7	110	105	0.34	0.40	45	13
8	95	94	0.62	0.67	720	450
9	68	72	0.44	0.46	1440	348
10	72	71	1.23	1.14	2205	-

headache, fatigue, and hair loss. Two patients had slightly increased levels of liver enzyme, but three patients initially had a slightly higher level of liver enzymes, which decreased during treatment.

From a clinical point of view, the results provide basic information, which will facilitate a larger scale study to further assess the role of anti-fungal medication in the treatment of sarcoidosis. Awaiting the results from such studies, anti-fungal medication could be considered in patients with corticosteroid-resistant disease. When side effects of corticosteroids are unacceptable, an anti-fungal medication should be the treatment of choice.

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