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The Treatment of Aspergillosis and Aspergilloma with Itraconazole, Clinical Results of an Open International Study (1982 - 1987)

Die Behandlung der Aspergillose und des Aspergilloms mit Itraconazol, Klinische Ergebnisse einer offenen internationalen Studie (1982 - 1987)

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Key words: Aspergillosis – aspergilloma – clinical treatment – itraconazole
Schlüsselwörter: Aspergillose – Aspergillom – klinische Behandlung – Itraconazol

Summary: A total of 137 patients with aspergillosis or aspergilloma has been treated with 50 to 400 mg itraconazole daily during 11 to 780 days.

The global assessments »markedly improved« and »cured« were given to 60 % of the treatments in invasive aspergillosis (n = 35) and reached 66 % in chronic necrotising pulmonary aspergillosis (n = 44). These response rates are sufficiently high regarding the limited number of antifungal agents useful in aspergillosis. Sixty-two percent of the chronic pulmonary aspergilloma cases (n = 42) showed symptomatic improvement and the radiological picture had improved in 30 %. In one patient, the fungus ball disappeared during long-term treatment. The results in five allergic bronchopulmonary aspergillosis (ABPA) patients indicate a possible role for itraconazole as complementary treatment to corticosteroids. All seven patients with cutaneous aspergillosis were mycologically and clinically cured after a maximum of 158 days of treatment. Two out of three biopsy proven cases of bone aspergillosis responded to itraconazole therapy. These long-term treatments with itraconazole were well tolerated. The reported side effects were merely of gastro-intestinal origin and there was no effect on the most important biochemical and haematological parameters.

Itraconazole appears to be a valuable new tool in the treatment of aspergillosis.

Zusammenfassung: Eine Gesamtzahl von 137 Aspergillose- und Aspergillom-Patienten wurde mit 50–400 mg Itraconazol täglich über Perioden zwischen 11 und 780 Tagen behandelt.

Das Globalurteil »wesentlich gebessert« oder »geheilt« erhielten 60 % der Behandelten mit invasiver Aspergillose (n = 35) und 66 % der Patienten mit chronisch nekrotisierender Lungenaspergillose (n = 44). Diese Ansprechquoten sind recht hoch, wenn man die beschränkte Anzahl der bei Aspergillose wirksamen Antimykotika berücksichtigt. Bei 62 % der Fälle mit

chronischem Lungenaspergillom (n = 42) wurde eine symptomatische Besserung erzielt, bei 30 % besserte sich das radiologische Bild. Bei einem Patienten verschwand der Fungusball während Langzeitbehandlung. Die Ergebnisse von 5 Patienten mit allergischer bronchopulmonaler Aspergilose (ABPA) deuten auf die mögliche Rolle von Itraconazol bei einer Kombinationsbehandlung mit Kortikosteroiden. Alle 7 Patienten mit kutaner Aspergillose waren nach einer maximalen Behandlungsdauer von 158 Tagen mykologisch und klinisch geheilt. Zwei von 3 bioptisch nachgewiesenen Fällen mit Knochenaspergillose sprachen auf Itraconazol-Behandlung an. Die Langzeitbehandlung mit Itraconazol war gut verträglich. Die angegebenen Nebenwirkungen waren meist gastrointestinalen Ursprunges, die wesentlichsten biochemischen und hämatologischen Parameter blieben unbeeinflußt. Damit erweist sich Itraconazol als ein wertvolles neues Medikament bei der Behandlung der Aspergillose.

Introduction

Itraconazole, a new oral triazole is active against *Aspergillus* spp. in vitro and in vivo (1, 2, 3). The molecular basis for itraconazole activity and the effect on the ultrastructure of *A. fumigatus* have been described previously (4, 5).

This report describes the actual results of an open international multicenter study. The analysis has been made starting from a heterogeneous series of case records. Moreover, criteria to determine the difference between colonization and infection or between invasive and chronic necrotizing pulmonary aspergillosis are debatable and often not realistic in clinical practice. Comparable criticism can be given concerning the subjective way of treatment evaluation.

The diagnosis of aspergillosis is divided into five groups:

I Invasive aspergillosis
II Chronic necrotising pulmonary aspergillosis
III Chronic pulmonary aspergilloma
IV Allergic bronchopulmonary aspergillosis
V Other types of aspergillosis

The results of itraconazole treatment in these five groups will be illustrated.

Patients and methods

All presented information was compiled using the same open protocol. Pregnant patients did not enter the trial. Patients receiving concomitant antifungal therapy or patients who could not be monitored properly were excluded.

At the moment of selection, the investigator made a complete clinical evaluation of the patient. The diagnosis was confirmed, depending on the nature of the disease by microscopy, culture, histology, serology, biopsy, radiography, endoscopy and/or scanning. Follow-up of the clinical and mycological parameters as well as biochemical monitoring, side effect reporting and global evaluation were the main elements of the patient record. Information about concomitant diseases, predisposing factors, concomitant medication, duration of disease and previous antifungal treatment was also documented.

The outcome of the itraconazole treatment was considered unevaluable when the duration of treatment was too short, i.e. less than 7 days, or when concomitant antifungals were used despite the exclusion criteria. A total of 137 patients with aspergillosis or aspergilloma has been treated with itraconazole in seven countries, with doses varying from 50 to 400 mg daily. Treatment duration varied from 11 days (a case of invasive aspergillosis) to 780 days (a case of aspergilloma).

Patient characteristics, concomitant diseases and predisposing factors of all evaluable patients are given in Table 1.

Table 1a: Patient characteristics of all evaluable patients

	Invasive aspergillosis (n = 35)	Chronic necrotosing pulmonary aspergillosis (n = 44)	Chronic pulmonary aspergilloma (n = 42)	Other types of aspergillosis (n = 11)	Allergic bronchopulmonary aspergillosis (n = 5)
Sex (Male/ Female)	17M/18F	22M/22F	26M/16F	7M/4F	1M/4F
Age: median (min-max) years	45 (2-75)	60 (15-88)	54 (15-88)	49 (6-66)	59 (12-83)
Duration of diseases median (min-max)	23 days (23 days – 7 years)	3 months (7 days – 14 years)	1.5 years (1 week – 13 years)	10 days (1 day – 23 years)	7 years (4 weeks – 30 years)

Table 1b: Predisposing factors of all evaluable patients

Invasive aspergillosis		**Chronic necrotising pulmonary aspergillosis**		**Chronic pulmonary aspergilloma**	
Immunosuppressive drugs	24	Corticosteroids	25	Old or active tuberculosis	15
Antibiotics	22	Antibiotics	15	Antibiotics	13
Corticosteroids	15	Surgery	5	Corticosteroids	7
Indwelling catheter	9	Radiotherapy	4	Catheter	6
Surgery	3	Catheter	4	Surgery	5
Occupation	2	Alcohol	4	Environment	5
Radiotherapy	3	Environment	3	Immunosuppressive drugs	5
Prosthesis	1	Immunosuppressive drugs	1	Alcoholism	2
Antivirals	1			Pneumothorax	1
				Radiotherapy	1
				Drug addict	1
				Smoker	1

Table 1c: Concomitant diseases of all evaluable patients

Invasive aspergillosis		Tuberculosis	5	Chronic pulmonary disease	7
Acute myeloid leukemia	11	Lung fibrosis	4	Acute myeloid leukemia	4
Acute lymphatic leukemia	6	Lung cancer	4	Emphysema	3
Leukemia	2	Bronchial asthma	3	Allergic bronchopulmonary	
Chronic lymphatic leukemia	3	Sarcoidosis	2	Aspergillosis	2
Chronic aspecific respiratory		Decubitus	1	Asthma	2
disease	1	Mucoviscidosis	1	Gastritis	1
Lung cancer	2	Testis cancer	1	Mammacarcinoma	1
Renal transplant	1	Laryngeal cancer	1	Chronic bronchitis	1
Immunosuppresion not spec.	5	Pneumonia	1	Malnutrition	1
Lymphoma	1	Cervical cancer	1	Silicosis	1
Astrocytoma	1	Pancreatitis	1	Atopy	1
Chronic granulomatous disease	1	Allergic bronchopulmonary		Diabetes-mellitus	1
Hodgkin's disease	1	Aspergillosis	1	Sarcoidosis	1
Colon cancer	1	Bechterew disease	1	Renal insufficiency	1
Medullar aplasia	1	Recklinghausen disease	1	Chronic granulomatous disease	1
		Hypertension	1	Pneumonia	1
		Cystic fibrosis	1	Duodenal ulcer	1
Chronic necrotising pulmonary aspergillosis		Bronchus carcinoma	1	Rheumatoid arthritis	1
				Chronic lymphatic leukemia	1
Chronic pulmonary disease	10				
Emphysema	6	**Chronic pulmonary aspergilloma**			
Diabetes-mellitus	6	Tuberculosis	15		

Table 2: Invasive aspergillosis treated with itraconazole (n = 35): previous therapy, confirmation of diagnosis and global assessment

Previous therapy		Confirmation of diagnosis	
Amphotericin B	25	Biopsy/Histology	8
		Culture/Microscopy	18
Flucytosine	9	Serology	7
		Serology/Culture	2
Ketoconazole	3	completed by	
		Radiography	26
None	9		

Global assessment	Number	Cause of death
Cure	9	
Marked improvement	12	– relapse leukemia
Moderate improvement	5	– lung bleeding – myocardial infarction – bacterial septicemia
Unchanged	2	
Deteriorated	7	– respiratory insufficiency – septic shock (streptococcal infection) – overwhelming infection – bacterial, fungal, viral infection – relapse acute myeloid leukemia – unknown – respiratory insufficiency

Results

Invasive aspergillosis

Thirty-five patients with invasive aspergillosis have been treated with itraconazole at a dosage varying from 100 mg to 400 mg daily and a treatment duration varying from 11 to 372 days.

In 25 patients amphotericin B was used as previous antifungal therapy and stopped for toxicity of inefficacy reasons. Almost 70 % of these patients had leukemia.

Immunosuppressive drugs, antibiotics and corticosteroids, were considered as the major predisposing factors for the development of invasive aspergillosis.

The respiratory tract was the site of infection in 28 cases. Blood (n = 2), liver, bone, CNS and the mucous membranes were the other sites. The global assessments marked improvement or cure were given to 21 treatments (60 %) (Table 2). For the eight biopsy proven cases, the response rate was the same: 63 %.

The symptoms (fever, cough, dyspnoe, weight loss, ...) were scored as absent (0), mild (1), moderate (2) or severe (3). Figure 1 illustrates the shift from a total symptom score 3 to a total score 0. Seventy-five percent of the patients where this evaluation was possible (n = 20) showed symptomatic improvement.

On the radiological picture, improvement was observed in 50 % of the available radiographies (n = 26) (Figure 2).

In 24 patients *Aspergillus* sp. was demonstrated mycologically. The mycological cure rate was 63 %.

Chronic necrotising pulmonary aspergillosis

Forty-four patients with chronic necrotising pulmonary aspergillosis have been

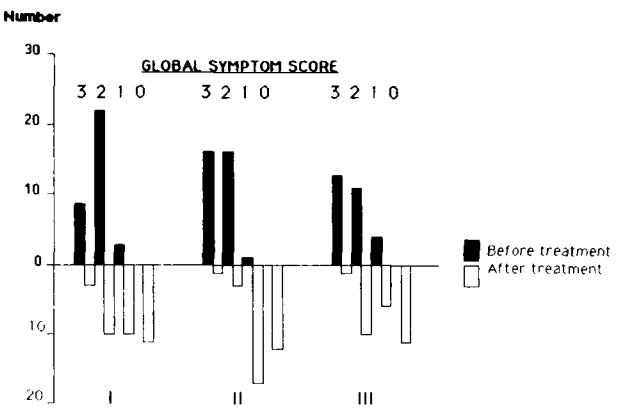

Fig. 1: Evolution of the global symptom score in chronic pulmonary aspergilloma (I, n = 34), chronic nerotising pulmonary aspergillosis (II, n = 33) and invasive aspergillosis (III, n = 28).

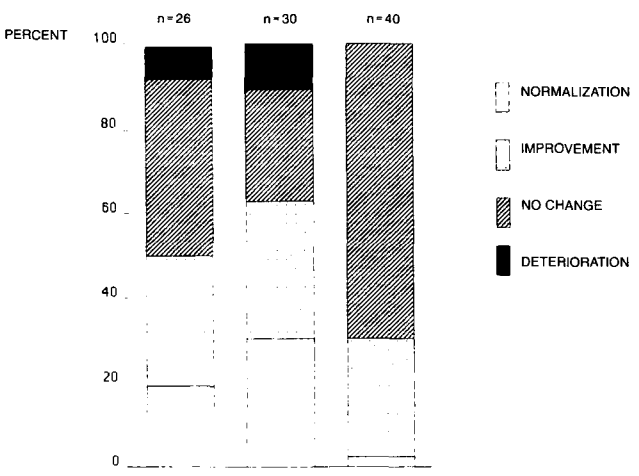

Fig. 2: Post-therapy radiological data in itraconazole treated patients with invasive aspergillosis (I), chronic necrotising pulmonary aspergillosis (II) and chronic pulmonary aspergilloma (III).

treated with itraconazole at a dosage varying from 100 mg to 400 mg daily and a treatment duration from 18 to 563 days. In 50 % of the cases, itraconazole was the first antifungal therapy. More than 60 % of the patients had an underlying chronic pulmonary disease. Corticosteroids and antibiotics were considered as the most important predisposing factors. Twenty-nine treatments resulted in marked improvement or cure (66 %) (Table 3).

The same evaluation of symptomatic improvement has been made as for invasive aspergillosis. (Figure 1) Symptomatic improvement was observed for 29 cases out of 33 where this evaluation was possible (88 %).

Figure 2 illustrates a radiological improvement in 63 % of the radiologically documented patients (n = 30). In 41 patients *Aspergillus* sp. was demonstrated mycologically. The mycological cure rate was 71 %.

Table 3: Chronic necrotising pulmonary aspergillosis treated with itraconazole (n = 44): previous therapy, confirmation of diagnosis and global assessment

Previous therapy		Confirmation of diagnosis	
Amphotericin B	9	Biopsy/Histology	4
Flucytosine	6	Culture/Microscopy	24
Natamycin	1	Culture/Serology	13
Ketoconazole	10	Serology	3
Miconazole	2	completed by	
Itraconazole	3	Radiography	30
None	23		
Global assessment	Number	Cause of death	
Cure	14		
Marked improvement	15		
Moderate improvement	10	– cancer – cardiac failure	
Unchanged	3		
Deteriorated	2	– respiratory insufficiency – respiratory insufficiency	

Chronic pulmonary aspergilloma

Forty-two patients with radiological evidence of aspergilloma have been treated with itraconazole at a dosage varying from 100 to 400 mg daily and with a treatment duration varying from 18 to 780 days.

The diagnosis was confirmed by serology (merely precipitins and Elisa) in 31 patients, and by mycological examination in 27 patients. Sixteen aspergillomas were built by *A. fumigatus*, one by *A. niger* and one by *A. nidulans*.

An old or active tuberculosis was the underlying pathology in 15 patients, while another 15 had chronic pulmonary disease.

The global assessments marked or moderate improvement, were given to 23 treatments (56.0 %) (Table 4). This global evaluation was a combination of the evolution of the radiological picture, the serological data and of the subjective symptoms.

The most important symptoms were cough, purulent sputum, weight loss, malaise, fever, pain, hemoptysis and dyspnoea. The combination of symptoms was scored as absent (0), mild (1), moderate (2) or severe (3). Figure 1 illustrates the diminuation of the total symptom score at the end of the treatment. Sixty-two percent of the evaluable patients (n = 34) showed symptomatic improvement. The radiological picture shows improvement in 30 % of the patients. This improvement resulted in the disappearence of the fungus ball in one patient, but was mostly a size reduction of the fungus ball (Figure 2).

Allergic bronchopulmonary aspergillosis

Five patients with allergic bronchopulmonary aspergillosis have been treated with 50 to 400 mg itraconazole daily for 43 to 239 days. All had underlying asthma, and the relationship with *Aspergillus* was made by positive immediate *Aspergillus* reactivity and/or by multiple positive sputum culture.

The diagnosis was confirmed by a combination of the following criteria: elevated total IgE, eosinophilia, positive precipitins to *A. fumigatus* and radiological findings.

The duration of the disease varied from 4 weeks to 30 years. The administration of itraconazole resulted in a remission stage of ABPA in two patients, and another two

Table 4: Chronic pulmonary aspergillosis treated with itraconazole (n = 42): previous therapy, confirmation of diagnosis and global assessment

Previous therapy		Confirmation of diagnosis	
None	25	Radiography/Scanning	42
Amphotericin B	13	completed by	
Flucytosine	6	Culture/Microscopy	27
Ketoconazole	3	Serology	31
Miconazole	1	Biopsy/Histology	5

Global assessment	Number	Cause of death
Marked improvement	17	
Moderate improvement	7	
Unchanged	12	
Deteriorated	6	– respiratory insufficiency – cardiac failure active aspergilloma – shock (respiratory insufficiency)

patients experienced moderate to marked improvement. The fifth patient did not change.

The concomitant use of oral corticosteroids was allowed and may also have contributed to the observed remission or improvement.

Nevertheless, sputum cultures became negative for each of the three cases where *A. fumigatus* was initially cultured. An overview of patient characteristics and treatment data is given in Table 5.

Other types of aspergillosis

**Aspergillus* skin infections were diagnosed in four cases.

A. fumigatus was identified in three patients, *A. flavus* was the causative organism for the fourth patient.

After a maximum of 2 months treatment with 100 to 400 mg itraconazole daily, the global evaluation was cured or markedly improved in all cases. In three cases, mycological examination was carried out at the end of therapy; there was no clinical sign of aspergillosis and cultures were negative.

*Two cases of otomycoses due to *A. fumigatus* were treated with 200 mg itraconazole daily for 34 and 36 days respectively. Both therapies resulted in clinical and mycological cure.

*In the seventh patient, *A. flavus* was the causative organism of a skin infection combined with onychomycosis. A treatment of 200 mg itraconazole daily during 158 days resulted in clinical and mycological cure.

*Out of three biopsy proven cases of bone aspergillosis, two responded after 52 and 199 days of therapy with 200 mg itraconazole daily. One case remained unchanged after 63 days with 100 to 400 mg daily. The sinus ethmoidalis was infected by *A. fumigatus* and treated with 400 mg itraconazole daily during 70 days. This treatment resulted in a clinical cure and negativation of the culture.

Safety with long-term itraconazole treatment

In the in house safety analysis of 137 long-term treated patients, 17.7 % re-

*Individual treatment data and patient characteristics of all patients are given in Table 6.

Table 5: Patient characteristics and itraconazole treatment data in five patients with allergic bronchopulmonary aspergillosis

Sex	Age	Weight	Length	Duration of disease	Start: Sputum culture	Treatment data	Global result	Sputum culture	Concomitant corticosteroids
F	50	54	157	30 years	A. fumigatus	400 mg 102 d. 150 mg 35 d. 100 mg 38 d. 50 mg 64 d.	remission	negative	prednisone
M	66	97	186	10 years	N.D.	100 mg 43 d.	remission	N.D.	none
F	83	—	—	4 weeks	A. fumigatus	100 mg 7 d. 200 mg 64 d.	mark.improv.	negative	cortisone
F	12	27	132	1.5 years	A. terreus	100 mg 102 d. 150 mg 59 d.	unchanged	A. terreus	prednisolone
F	59	50	153	7 years	A. fumigatus	200 mg 183 d.	mod.improv.	negative	prednisone

ported adverse experiences. Dyspepsia, abdominal pain, nausea, diarrhoea and dizziness were the most common adverse experiences. These adverse experiences were generally not severe despite the often general condition of many patients.

On the basis of the combined analysis of haematological and biochemical determinations in 137 patients on long-term therapy, it could be concluded that itraconazole at daily doses of 100, 200 and 400 mg is devoid of obvious drug-related effects on clinical laboratory parameters.

Discussion

Invasive aspergillosis

The ideal situation to evaluate the role of a new antifungal in invasive aspergillosis is to prove the invasive presence of *Aspergillus* sp. by tissue biopsy and to illustrate its absence after treatment by biopsy again.

In clinical practice, one can only try to achieve this goal. In invasive aspergillosis, often one has to be satisfied when a diagnosis can be made antemortem (6, 7). This is the reason why patients entered the study on mycological evidence without biopsy. The presence of *Aspergillus sp.* was documented in all patients by serology and/or mycological examination (8). Nevertheless, eight included cases were biopsy proven, and the response rate in this group (63 %) equals the response rate in the nonbiopsy proven cases of invasive aspergillosis.

Chronic necrotising pulmonary aspergillosis

In not immunocompromised patients the risk for invasive aspergillosis is much lower compared to immunocompromised patients.

Therefore, it should be easier to treat a chronic necrotising pulmonary aspergillosis. This is reflected by the previous antifungals given to these patients. Only 20 % of the patients received amphotericin B treatment compared to more than 70 % in invasive aspergillosis.

The results with itraconazole confirm this idea. Indeed, the results in all used efficacy criteria were higher, although not statistically significant, for chronic necrotising pulmonary aspergillosis than for invasive aspergillosis. With a response rate of 66 % and symptomatic improvement in 88 % of the treated patients, itraconazole seems to be effective in the treatment of chronic necrotising pulmonary aspergillosis.

With the exception of amphotericin B, the other chemotherapeutic possibilities are disappointing. The oral administration of

Table 6: Patients characteristics and itraconazole treatment data in eleven patients with other types of aspergillosis

Site of infection	Sex	Age	Weight	Length	Duration of infection	Organism	Treatment data		Global result	Mycol. result
Skin	M	6	26	127	1 week	A. flavus	150-200 mg	46 d.	cure	negative
Skin	M	11	48	151	2 weeks	A. fumigatus	200 mg	42 d.	cure	negative
Skin	M	58	85	184	1 week	A. fumigatus	100-150 mg	64 d.	cure	negative
Skin	F	66	77	164	4 weeks	A. fumigatus	200-400 mg	26 d.	marked impr.	N.D.
Skin + nails	M	9	40	151	10 days	A. flavus	200 mg	158 d.	cure	negative
Ear	F	33	84	–	6 weeks	A. fumigatus	200 mg	36 d.	cure	negative
Ear	F	49	71	144	1 day	A. fumigatus	100-200 mg	34 d.	cure	negative
Bone	M	45	77	180	23 years	A. fumigatus	100-200 mg	199 d.	cure	negative
Bone	M	52	53	171	2 years	A. fumigatus	200 mg	52 d.	marked impr.	negative
Bone	M	60	79	168	1 week	A. fumigatus	100-400 mg	63 d.	unchanged	A. fumigatus
Sinus ethmoidalis	F	56	–	–	12 months	A. fumigatus	400 mg	70 d.	cure	negative

itraconazole could certainly offer a valuable alternative to amphotericin B. In more than 40 % (9, 10) of the itraconazole cases previous amphotericin B therapy had been stopped for adverse experiences or inefficacy. It is essential to start itraconazole therapy as soon as possible, especially in cases of invasive aspergillosis, where morbidity and mortality are high.

Chronic pulmonary aspergilloma

Antifungal therapy in chronic pulmonary aspergilloma has not been very successfull until now (11). Nevertheless, the treatment with oral itraconazole has been able to destroy the fungus ball in one patient. This disappearance coincided with serological and symptomatic improvement which could indicate that itraconazole was responsable and the disappearance was not spontaneous. However, in all other patients itraconazole therapy did not result in the resolution of the fungus ball, and radiological improvement was observed in only 12 patients (30 %).

The most important aspect, and the reason why itraconazole therapy could be advised in a non-operable aspergilloma is the effect on the clinical signs and symptoms, combined with a decrease in precipitins. Improvement of the general symptom score in 62 % of the treated cases suggested itraconazole as a valuable treatment for patients suffering from their aspergilloma. In 32 % of the patients all symptoms disappeared. Itraconazole was found to be a safe therapy in long-term treatment in this serie of aspergilloma (12).

Allergic bronchopulmonary aspergillosis

Because of the allergic nature of this disease, it can be expected that antifungal therapy alone will not cure an allergic bronchopulmonary aspergillosis (13). The *Aspergillus* species is only the provoking factor. However, the present results suggest that itraconazole therapy may be considered as a valuable additional therapy to the classical corticosteroids to get an an exacerbation of ABPA into remission or as a long-term maintenance therapy to prevent exacerbations or to reduce symptoms especially when the risk of inhaling *Aspergillus* spores is high (14). A large scale comparative trial is essential to determine the real value of itraconazole in ABPA, compared to corticosteroid therapy or in combination with corticosteroid therapy.

Other types of aspergillosis

The results in cutaneous aspergillosis suggest a therapeutic effect of itraconazole

against *Aspergillus*. All cultures became negative during treatment. Also the nail infection with *A. flavus* was cured after no more than 5 months of treatment. For skin infections with *Aspergillus*, a 2 month treatment with 200 mg daily may be suggested. Long-term treatment with 100 to 400 mg daily in bone aspergillosis and infections of the sinuses appears to be beneficial.

Conclusions

Itraconazole seems to be effective in the treatment of systemic and superficial aspergillosis and could be useful in the management of non-operable aspergilloma or as an additional treatment in allergic bronchopulmonary aspergillosis.

Moreover, the long term use of itraconazole appears to be safe and well tolerated.

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