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REVIEW

Itraconazole in the Treatment of Nonfungal Cutaneous Diseases: A Review

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ABSTRACT

Introduction: The anti-inflammatory and prokinetic properties of antibiotics have been widely reported. However, the non-antifungal properties of antifungal agents are less well known and less explored in clinical practice. The purpose of this review was to survey the literature on the non-antifungal use of itraconazole in dermatological practice and the possible modes of action of this agent.
Methods: The PubMed database was searched for relevant articles published up to January 2017. The references in the articles identified by the search were then hand-searched for additional relevant publications.
Results: Itraconazole displays a great diversity of non-antifungal activity and has been used to treat a broad spectrum of diseases. The results of our survey reveal that itraconazole has the potential to be an alternative agent for treating patients with advanced cancer (either alone or in combination with other cytotoxic chemotherapeutic drugs), especially those refractory to traditional treatments. Moreover, itraconazole acts as an anti-angiogenesis agent, induces nail growth, and modulates inflammatory or immune diseases.
Conclusion: Oral antifungal agents have many non-antifungal properties. However, the body of evidence on individual agents often remains limited due to the lack of large-scale randomized controlled studies. Although some of the findings published to date seem promising, pharmacological vigilance should be taken for off-label use in real-world practice.

Keywords: Itraconazole; Non-antifungal; Off-label use

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INTRODUCTION

Exploration of the possible therapeutic uses of medications beyond their official indications is of great interest in clinical practice. Among dermatologists, the off-label use of pharmaceutical drugs is prevalent given the rarity of many cutaneous disorders [1]. In addition, many dermatoses are considered to be trivial, with the result that they become "orphan diseases" with no medications approved for treatment of the indication. The anti-inflammatory activities of antimicrobials have been widely reported [2–4],

Table 1 Mechanism of itraconazole in treatment of dermatologic diseases

Action	Supposed mechanisms	Utilization in nonfungal skin disorders
Anti-malignancy	Anti-Hedgehog signaling pathway; target site on Smoothened	Advanced basal cell carcinoma
Anti-angiogenesis	Inhibition of endothelial cell migration, proliferation, and tube formation via blocking of VEGFR2 trafficking and signaling	Infantile hemangioma
		Keloid and hypertrophic scar
Anti-inflammation and immunomodulation	Suppression of T-lymphocyte proliferation	Mycosis fungoides
	Phenylpiperazine ring of ITZ related to the immunosuppressive effect	Lichen planus
		HIV-associated eosinophilic folliculitis
		Sarcoidosis
	Inhibition of neutrophil chemotaxis and movement	Palmoplantar pustulosis
	Inhibition of interleukin-8 production	
	Inhibition of the formation of pro-inflammatory metabolites (i.e., 5-lipoxygenase)	
Induction of nail growth	Acceleration of nail matrix turnover rate	Yellow nail syndrome
Reduction of hypersensitivity reaction	Modulation of *Malassezia* species (as an allergen)-induced hypersensitivity reaction	Head and neck dermatitis or refractory atopic dermatitis
		Reducing irritation of calcipotriol on scalp psoriasis

HIV human immunodeficiency virus, *ITZ* itraconazole, *VEGFR2* vascular endothelial growth factor receptor 2

but the non-antifungal activities of antifungal agents are less well known. In this review, we explore the possible non-antifungal use of itraconazole in dermatology and discuss the possible modes of action of this agent (Table 1).

METHODS

A literature search of the PubMed database was conducted for relevant articles published up to 2017 using the search terms 'itraconazole' AND 'dermatosis,' but NOT 'fungal,' NOT 'dermatophyte,' and NOT 'onychomycosis.' We also included papers identified by hand-searching the references of the articles identified in the literature search. Articles reporting non-dermatological uses and treatment mechanisms mainly focusing on antifungal effects (e.g., itraconazole in seborrheic dermatitis) were excluded from the review.

This study is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Table 2 Studies and case reports on the use of itraconazole in dermatologic diseases

Disease	Dose regimen	Type of study and number of patients	Response to treatment	References
Advanced basal cell carcinoma	ITZ Three groups: (a) 400 mg/day for 1 month (b) 200 mg/day for 1–4 months (c) Control	Cohort study, phase II trial, n = 29 (n: a = 15, b = 4, c = 10)	45% decrease in cell proliferation; 24% decrease in tumor area	Kim et al. [8]
Infantile hemangioma	ITZ 5 mg/kg/day for 2–9 weeks	Case series, n = 6	All showed at least partial response in the first month; significant improvement after 3 months observation	Ran et al. [11]
Keloid and hypertrophic scar	ITZ for 2–4 weeks	Case series, n = 3	Improved dramatically	Okada and Maruyama [12]
Palmoplantar pustulosis	Two weeks of ITZ 100 mg/day, then maintenance dose of 50 mg/day, 100 mg every other day, or 100 mg/50 mg alternatively	One anecdotal report (n = 7) and another single, active-arm study (n = 6)	Complete resolution of pustules	Mihara et al. [14] V'lckova-Laskoska et al. [15]
HIV-associated eosinophilic folliculitis	ITZ 200–400 mg/day for 2 weeks	Single-arm, open trial, n = 28	61% of cases showed complete clearance and 14% of cases showed partial response	Berger et al. [16]
Lichen planus, eruptive extensive type	Pulsed oral ITZ 200 mg, bid, 1 week in each month for a total of 3 months	Prospective, open-labelled study, n = 16	77% of cases ceased to develop; 55% of patients had no itch; 33% of cases showed complete flattening	Khandpur et al. [18]
Sarcoidosis	ITZ, fluconazole, or KTZ 200 mg/day + corticosteroids for 3–6 months	Single-arm, n = 18 (ITZ = 9, KTZ = 1, fluconazole = 8)	Significant reduction in number of lung lesions	Tercelj et al. [19]
Mycosis fungoides	ITZ 200 mg/day for 7 days	Case report, n = 1	Completely subsided	Cooper et al. [20]

Table 2 continued

Disease	Dose regimen	Type of study and number of patients	Response to treatment	References
Yellow nail syndrome	ITZ 400 mg/day, 1 week in each month for a total of 7 cycles, + vitamin E	Case report, $n = 1$	Marked ungual regrowth	Luyten et al. [25]
	ITZ 400 mg/day, 1 week in each month for a total of 6–12 months	Case series, $n = 8$	Two cases cured; 2 cases improved a little; 4 cases showed no response	Tosti et al. [27]
Head and neck dermatitis (HND) or refractory atopic dermatitis	(1) ITZ 200 mg/d initially, then six patients were shifted to fluconazole 200 mg/day or KTZ 200 mg/day due to the insurance, total 2 months (2) Maintenance phase: azole 200 mg, biw; for a total of 8 months	Retrospective descriptive study, $n = 24$	17 cases (71%) responded	Kaffenberger et al. [28]
	Three groups: (a) ITZ 200 mg/day (b) ITZ 400 mg/day (c) Placebo all for 7 days	RCT, double-blind, $n = 53$ (n: a = 18, b = 17, c = 18)	SCORAD improved prominently	Svejgaard et al. [29]
	Two groups: (a) ITZ 100 mg/day + lactobacillus preparation for 8 weeks (b) *Lactobacillus* preparation alone for 8 weeks; then shift to the opposite regimen for another 8 weeks	RCT, cross-over study, $n = 34$	Both groups decreased use of topical steroids, eosinophils, and serum immunoglobulin E levels	Ikezawa et al. [30]
Reducing irritation of calcipotriol on scalp psoriasis	ITZ 100 mg/day for 8 weeks	RCT, double-blind, $n = 137$	Local irritation: 19% (ITZ) vs. 47% (placebo), $p < 0.001$	Faergemann et al. [32]

bid Twice per day, *biw* twice weekly, *KTZ* ketoconazole, *RCT* Randomized controlled trial, *SCORAD* Scoring atopic dermatitis

ITRACONAZOLE

Itraconazole, a triazole antifungal medication, was approved by the United States Food and Drug Administration in 1992.

Anti-Hedgehog Signaling Pathway, Anti-Angiogenesis, and Reverse Drug Resistance

Itraconazole has been used to treat a variety of advanced cancers. Three mechanisms have been proposed for this antifungal medication: (1) the anti-Hedgehog (Hh) pathway; (2) anti-angiogenesis; and (3) enhancement of some cytotoxic chemotherapy agents by reversing P-glycoprotein-related resistance. The P-glycoprotein is present in some cancer cells to pump out chemotherapy drugs.

Basal Cell Carcinoma

Itraconazole has been investigated for its potential in managing advanced basal cell carcinomas (BCCs). Distinct from the antifungal mechanism of inhibiting ergosterol synthesis, the anti-Hh pathway is the main target of BCCs. Hydroxy-itraconazole, a metabolite of itraconazole, also inhibits the Hh pathway [5]. The molecular target of itraconazole is on Smoothened (SMO), a G protein-coupled receptor, but the site is distinct from that of cyclopamine and other SMO antagonists [6], which explains its effect on diseases resistant to currently available SMO antagonists. Itraconazole can be used synergistically with other SMO antagonists to control tumors. In 2010, itraconazole was demonstrated to be a Hh inhibitor in murine medulloblastoma and BCC; this was followed by an increase in the number of clinical human trials on itraconazole in a variety of cancer therapies [5, 7].

Kim et al. conducted an open-label, phase II trial to evaluate the efficacy of itraconazole in suppressing BCCs [8]. In this trial, 29 patients were allocated to two active treatment groups receiving various doses of itraconazole and one placebo-controlled group (Table 2). The results showed a decrease of 45% in cell proliferation (biomarker: ki67), of 65% in Hh pathway activity (biomarker: GLI1 [glioma-associated oncogene homolog 1] mRNA), and of 24% in tumor area among patients treated with itraconazole. Both participants in the placebo-controlled group and patients with a history of previous exposure to vismodegib showed no reduction in tumor size, cell proliferation, or Hh pathway activity. This trial confirmed the anti-BCC activity of itraconazole in humans; however, the optimal itraconazole dosing regimen, long-term outcome, and efficacy compared to vismodegib still need further investigation [8].

Anti-Angiogenesis

The anti-angiogenesis characteristic of itraconazole was discovered by screening the drug library and then it was authenticated in vitro and in murine non-small-cell lung carcinoma xenograft models [9]. The results suggest that itraconazole inhibits endothelial cell migration, proliferation, and tube formation via inhibition of vascular endothelial growth factor receptor 2 (VEGFR2) trafficking and signaling [10]. Dermatological examples utilizing the anti-angiogenesis activity of itraconazole include a case series of infantile hemangioma [11] and keloid treatment [12, 13].

Infantile Hemangioma

In a published case series, six infants aged 2–5 months old were treated successfully with oral itraconazole 5 mg/kg per day for their infantile hemangioma. The treatment period was 2–9 weeks, and the mean follow-up time was 9.7 months. Two of the patients had local ulcers and secondary candida infection on the hemangioma lesion. All patients experienced at least partial response in the first month and significant improvement after 3 months. Few adverse events were detected, with only two cases of mild diarrhea which subsided without drug cessation [11].

Keloid and Hypertrophic Scar

Okada et al. reported three cases of keloids ($n = 2$) and hypertrophic scar ($n = 1$); all three patients showed dramatic improvement following oral itraconazole therapy for 2–4 weeks for the treatment of onychomycosis and tinea

pedis [12]. These authors reported that the efficacy of itraconazole might be attributed to the relationship between keloids and fungal infection. On the other hand, Chui et al. proposed that the possible mechanism was based on inhibition of fibroblast growth factors and VEGFs which are involved in the pathogenesis of keloids and hypertrophic scars [13].

Anti-Inflammatory and Immunomodulatory Properties

Palmoplantar Pustulosis

One anecdotal report ($n = 7$) and another single, active-arm study ($n = 6$) demonstrated itraconazole as an effective treatment for palmoplantar pustulosis (PPP). In both studies, all patients experienced complete resolution of pustules after taking itraconazole 100 mg/day for 2 weeks. Erythema and desquamation improved either modestly or significantly. However, all patients showed a relapse of all lesions within 1 month of discontinuation of itraconazole. Thus, a maintenance dose of 50 mg/day, 100 mg every other day, or 100 mg/50 mg alternatively was administered in some patients until stable remission was achieved. There were no adverse events noted. A possible mechanism of itraconazole in PPP is the anti-inflammatory effect. Specifically, itraconazole inhibits neutrophil chemotaxis, interleukin-8 production, and the formation of pro-inflammatory metabolites (i.e., 5-lipoxygenase) [14, 15].

Human Immunodeficiency Virus-Associated Eosinophilic Folliculitis

A single-arm, open trial enrolled 28 patients with human immunodeficiency virus-associated eosinophilic folliculitis [16]. Of these 28 patients, 61% had complete clearance within 2 weeks, and 14% experienced partial response. The initial itraconazole dose was 200–400 mg/day for 2 weeks; if the optimal condition was not achieved, the dose of 200 mg/day was increased to 400 mg/day. In this trial, three patients were shifted to fluconazole due to adverse events or cryptococcal infection; none of them showed improvement. The authors speculated that the reason itraconazole was effective but fluconazole was not might be due to the anti-inflammatory effect of itraconazole rather than to its antifungal effect [16].

Lichen Planus

Libow et al. were the first to report the use of itraconazole to treat lichen planus (LP) in 1998 [18]. Of the four patients in their study, two experienced complete clearance of lesions following the initiation of itraconazole treatment and two had partial response [17]. In 2009, Khandpur et al. recruited 16 patients with eruptive extensive LP to verify itraconazole as an alternative treatment for this form of LP [18]. This prospective, open-label study was designed to give pulsed oral itraconazole 200 mg twice daily for 1 week in each month to the patients. After 3 months, the results showed that itraconazole was very effective in treating eruptive LP. New lesions ceased to develop in 77.77% of subjects, 55.55% of patients showed alleviation of pruritus, and 33.33% of patients showed a complete flattening of lesions within 3 months [18].

Sarcoidosis

Tercelj et al. designed a single-arm, interventional study to which they recruited 18 patients with stage II or III sarcoidosis to receive antifungal agents (itraconazole, fluconazole, or ketoconazole 200 mg/day) together with corticosteroid (at usual dose, as mentioned in the article) treatment for 3–6 months [19]. Patients who had previously received prednisolone 12 mg or 16 mg every other day for at least 6 months with poor clinical improvement or who had a sarcoidosis relapse after discontinuation of corticosteroid therapy were enrolled in this study. The results revealed a highly significant reduction in pulmonary infiltration based on X-ray scores, significant amelioration in diffusion capacity, and significant improvement in the severity of symptoms, including cough, dyspnea, chest pain, and persistent fever of $> 37\,^{\circ}C$. The mechanism was reported to be associated with an unknown immune effect. Because no fungi were identified in the lung biopsy, the authors suggested that the

antifungal medications used to treat sarcoidosis do not work directly on the synthesis of the fungal cell membrane [19]. However, the use of itraconazole in cutaneous sarcoidosis treatment has not yet been reported.

Mycosis Fungoides

A good response to itraconazole 200 mg/day for 7 days was reported in a patient with pathology-confirmed plaque-stage mycosis fungoides [20]. Lesions completely subsided within 1 week. The lesions relapsed in the following and third years but again cleared within 1 week of itraconazole therapy. The authors proposed that the possible mechanism is related to the immunomodulatory activity of itraconazole [20]. In previous studies, itraconazole was proven to inhibit T-lymphocyte proliferations in vitro [21] and to have anti-inflammatory effects in vivo [22].

Various studies have revealed that the potency of azole antifungal agents, especially itraconazole, in suppressing T-lymphocyte proliferation is similar to that of cyclosporine, but that interferon-γ and tumor necrosis factor-α were not significantly blocked by azole agents [21, 23]. It has been suggested that the phenylpiperazine ring of itraconazole contributes to the anti-inflammatory activity [24]. The immunosuppressive effect might explain the treatment efficacy of itraconazole in inflammatory diseases such as mycosis fungoides and LP.

Induction of Nail Growth

Yellow Nail Syndrome

A 27-year-old woman diagnosed with yellow nail syndrome unexpectedly experienced better ungual regrowth after itraconazole pulse therapy (400 mg/day, 1 week per month) was added to her vitamin E (800 IU per day) therapy for secondary onychomycosis [25]. The initial 6 months of treatment with vitamin E alone showed only mild improvement of proximal nail growth. After 4 cycles of combined itraconazole and vitamin E therapy, the finger nails improved considerably [25]. The mechanism probably involved the acceleration of nail growth rate by itraconazole, an effect which has been observed in a number of in vivo studies. Doncker et al. found higher nail peaks and a larger mean roughness value, indicating that itraconazole had induced a quicker nail matrix turnover rate, as noted by optical profilometry [26].

However, another eight-case report demonstrated no apparent effect of itraconazole on yellow nail syndrome. In that study, oral itraconazole was administered 400 mg/day, 1 week every month, for at least 6 months. If the nails showed improvement, the treatment time was extended to 12 months. Of the eight patients two were cured and another two showed slight improvement; no improvement was observed for the remaining four patients, and one of these even improvedr after the therapy was changed vitamin E 1200 mg/day for 6 months [27].

Reduction of the Hypersensitivity Reaction

Head and Neck Dermatitis or Refractory Atopic Dermatitis

Itraconazole is an effective treatment for refractory atopic dermatitis, especially the unique subtype of head and neck dermatitis (HND). The treatment mechanism has been related to the hypersensitivity reaction to *Malassezia* species in these sebum-rich areas. In the relevant literature, the initial dose ranges from 100 to 400 mg/day for 1–2 weeks. A maintenance phase consisting of a weekly-based regimen should be continued to reduce recurrences. Optimal maintenance dosing regimens still need to be investigated.

One retrospective study involving 24 patients with HND reported that 17 of the patients (71%) responded to a 2-month-long treatment with an oral azole antifungal [28]. All patients were treated with itraconazole 200 mg/day at the start of the treatment regimen, but six were subsequently switched to fluconazole 200 mg/day or ketoconazole 200 mg/day due to healthcare insurance or cost issues. However, a high discontinuation rate during pulse therapy with ITZ 200 mg twice weekly (maintenance phase) suggested that the cephalic type of atopic dermatitis might be induced by hypersensitivity of the *Malassezia*

species rather than by the mere overgrowth of yeasts as occurs in seborrheic dermatitis or tinea versicolor. The authors inferred that because only a small amount of allergen could induce a prolonged hypersensitivity reaction, the twice-weekly regimen during the maintenance phase might lead to dose insufficiency that was unable to control the HND [28].

One randomized controlled trial (RCT) ($n = 53$ patients) revealed the significant efficacy of a 7-day-long therapeutic regimen of itraconazole at both 200 and 400 mg/day compared with placebo in patients with HND. Regardless of prick tests to *Malassezia* antigens, itraconazole clearly improved the SCORAD index. However, other areas of body surface showed no significant improvement by global evaluation [29].

Ikezawa et al. conducted a cross-over RCT which recruited 34 subjects with refractory atopic dermatitis and a positive radioallergosorbent test (RAST) to *Malassezia* [30]. The subjects were distributed into two groups (A and B). Group A was given itraconazole + *Lactobacillus* preparation for 8 weeks, then the *Lactobacillus* preparation alone for the following 8 weeks. Group B was given the *Lactobacillus* preparation alone for 8 weeks, then a combination of itraconazole + *Lactobacillus* preparation for the following 8 weeks. The dosage of itraconazole was 100 mg/day in both groups. The results revealed that eosinophil counts, serum immunoglobulin E (IgE) levels, specific IgE titers to *Malassezia*, and the potency or dose of concomitant topical steroids had all declined significantly at the end of the itraconazole treatment in group A and group B [30].

For the treatment of chronic atopic dermatitis [31], Sugita et al. proposed a regimen of itraconazole 100 mg/day for 1 week, followed by itraconazole 200 mg/week for a further 11 weeks. These authors reported that at least 3 months of treatment were required to reduce recurrence for chronic atopic dermatitis.

Reducing Irritation of Calcipotriol on Scalp Psoriasis

A double-blind, randomized, placebo-controlled study ($n = 137$ subjects) reported that the elimination of *Malassezia* by itraconazole 100 mg/day for 8 weeks significantly reduced the irritation caused by the calcipotriol solution during the treatment of scalp psoriasis (local skin irritation: 19.4% [itraconazole] vs. 47.1% [placebo]; $p < 0.001$) [32].

Dosing

The approved dose of itraconazole is 200–400 mg per day for the treatment of fungal diseases. In the studies identified in our literature search, the dose of itraconazole used to treat non-antifungal cutaneous diseases was all within this range. No serious or new adverse effects were reported. However, we still recommend close surveillance of patients using this drug for the risks of liver dysfunction, heart failure, drug–drug interaction, and thrombocytopenia.

CONCLUSIONS

In conclusion, itraconazole possesses many non-antifungal properties. However, the body of evidence on these properties remains somewhat limited due to the lack of large-scale RCTs. The case numbers in some studies are rather small, and the proposed mechanisms still need to be verified. Nevertheless, this review of published studies reveals that itraconazole may have the potential to provide better control of difficult-to-treat diseases and give directions for further investigative studies. Although some of the findings reported herein seem exciting, care should be taken when using itraconazole for these off-label indications in real-world practice.

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