Itraconazole in the Treatment of Nonfungal Cutaneous Diseases: A Review

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ABSTRACT

Introduction: The anti-inflammatory and pro-kinetic 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

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],
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 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                                              |
| Anti-inflammation and immunomodulation | Suppression of T-lymphocyte proliferation<br>Phenylpiperazine ring of ITZ related to the immunosuppressive effect | Mycosis fungoides<br>Lichen planus<br>HIV-associated eosinophilic folliculitis<br>Sarcoidosis<br>Palmoplantar pustulosis |
|                                 | Inhibition of neutrophil chemotaxis and movement<br>Inhibition of interleukin-8 production<br>Inhibition of the formation of pro-inflammatory metabolites (i.e., 5-lipoxygenase) | Palmoplantar pustulosis<br>Palmoplantar pustulosis<br>Induction of nail growth<br>Modulation of Malassezia species (as an allergen)-induced hypersensitivity reaction | Yellow nail syndrome<br>Head and neck dermatitis or refractory atop dermatitis<br>Reducing irritation of calcipotriol on scalp psoriasis |

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

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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                          |                                                                                      |             |
| 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] |
| 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] |
| Sarcomiosis                            | ITZ, fluconazole, or KTZ              | Single-arm, n = 18                   | 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] |
| 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 | Retrospective descriptive study, n = 24 | 17 cases (71%) responded                     | Kaffenberger et al. [28]    |
|                                              | (2) Maintenance phase: azole 200 mg, biw; for a total of 8 months            |                                     |                                              |                             |
| Three groups:                                |                                                                              |                                     |                                              |                             |
| (a) ITZ 200 mg/day                          | RCT, double-blind, n = 53 (n: a = 18, b = 17, c = 18)                       | SCORAD improved prominently         | Svejgaard et al. [29]                      |
| (b) ITZ 400 mg/day                          |                                                                              |                                     |                                              |                             |
| (c) Placebo                                 | Two groups: RCT, cross-over study, n = 34                                    | Both groups decreased use of topical steroids, eosinophils, and serum immunoglobulin E levels | Ikezawa et al. [30]          |
|                                              |                                                                              |                                     |                                              |                             |
| (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 |                                                                              |                                     |                                              |                             |
| 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
peidis [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 \(>37\, ^\circ \text{C}\). 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 improved 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 \textit{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 \textit{Malassezia} [30]. The subjects were distributed into two groups (A and B). Group A was given itraconazole + \textit{Lactobacillus} preparation for 8 weeks, then the \textit{Lactobacillus} preparation alone for the following 8 weeks. Group B was given the \textit{Lactobacillus} preparation alone for 8 weeks, then a combination of itraconazole + \textit{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 \textit{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.

\textbf{Reducing Irritation of Calcipotriol on Scalp Psoriasis}

A double-blind, randomized, placebo-controlled study \((n = 137\) subjects) reported that the elimination of \textit{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].

\textbf{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.

\textbf{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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**Data Availability.** This article has no associated data or the data will not be deposited.

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