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REVIEW ARTICLE

Skin Allergy to Azole Antifungal Agents for Systemic Use: A Review of the Literature

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Abstract: ***Background***: Antifungal azoles are the first-line agents used to treat topical and, above all, systemic mycosis. The latter could be life-threating infections in immunocompromised patients. Chemotherapeutic antibiotics, including antifungal azoles, may induce hypersensitivity reactions; however, such immunologic adverse reactions have not been defined and carefully investigated.

Objective: The study aimed to provide an update on the evaluation and diagnosis of skin allergy to azole antifungal agents.

Methods: This is a systematic review performed on PubMed and Google Schoolbarusing using the key terms "allergy, hypersensitivity, anaphylaxis, immediate-type reaction, delayed-type reaction, ketoconazole, fluconazole, posaconazole, voriconazole, itraconazole, triazoles, imidazoles, antifungals, antimycotics". The search strategy included meta-analyses, randomized controlled trials, clinical trials, observational studies, reviews and case reports.

Results: One hundred twenty-four articles matched our search terms. The most common adverse events reported were T-cell mediated delayed-type hypersensitivity reactions, such as fixed drug eruptions, localized, generalized and exanthematous dermatitis, Steven-Johnson syndrome, toxic epidermal necrolysis and acute generalized exhanthematous pustulosis. Rarely a drug rash, eosinophilia systemic symptoms, has been described. Also, immediate-type reactions such as urticaria-angioedema or anaphylaxis have been reported following the administration of antifungal imidazoles, although not so frequently.

Conclusion: Despite their widespread use, triazoles seem to induce rare cutaneous hypersensitivity reactions, but the pathomechanisms, risk factors, diagnostic and management strategies, including skin tests and challenge tests, are little known and poorly investigated.

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1. INTRODUCTION

Fungal infections are not as frequent as bacterial and viral infections; nevertheless, there are high incidence of these infections in humans in the last 25 years, largely as a consequence of the increased number of immunocompromised patients, such as patients infected by Human Immunedeficiency Virus (HIV), transplant patients and critically ill patients in High Intensive Care Units. Furthermore, in these years, the antimycotic weaponry has increased considerably, since many new antifungal molecules have been added, as shown in Table **1**.

Azole antifungal agents are the largest and the most efficient class of synthetic antimycotics that can be used efficaciously to treat localized and generalized candidosis, cryptococcosis, histoplasmosis, pulmonary and systemic aspergillosis, dermatophytes, coccidioidomycosis, blastomycosis, penicilliosis, sporotrichosis and mucormycosis [1].

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Table 1. Antimycotic Agents for Systemic Use.

Macrolides: Amphoteicin B, nystatin
Antimetabolite: Flucytosine
Cytoskeleton Agent: Griseofulvin
Azoles: Imidazoles, triazoles
Allylamine: Terbinafine, naftifine
Echinocandin: Caspofungin, micafungin, anidulafungin

The above-listed fungal infections usually affect immune-compromised patients such as Human Immunodeficiency Virus (HIV)-infected subjects, oncologic, hematologic and critically ill patients and last but not the least, transplant patients. Neutropenia induced by chemotherapies places these patients at risk of serious fungal infections, most commonly with *Candida* species.

Systemic fungal infections are more serious because they are more difficult to diagnose, more likely to become chronic and may become life-threatening conditions. Prophylactic treatment is sometimes indicated in HIV-patients and bone-marrow transplant patients despite the high risk of inducing antibiotic resistance.

Even if new antifungals are available, triazoles are still considered the first- line drugs to treat systemic fungal infections and these are the most suitable and manageable drugs for patients to use at home.

Although about 20 azole antifungal chemotherapeutics are currently available in the market, most of them are mainly for topical use. They are classified into two groups: Azoles with two nitrogen atoms in the azole ring (the imidazoles including clotrimazole, econazole, ketoconazole, miconazole, and tioconazole) and those with three nitrogen atoms in the azole ring (the triazoles, of which fluconazole is the most representative of the class, followed by itraconazole, posaconazole, voriconazole and more recent isavuconazole). The bioisosteric triazole ring has achieved higher selectivity of fungal targets versus host [2].

There are three general mechanisms of action of antifungal agents: Cell membrane disruption, inhibition of cell division and inhibition of cell wall formation.

Antifungal activity stems from the presence of an aromatic five-member heterocyclic, either an imidazole or a triazole. Ketoconazole was the first imidazole molecule, introduced in 1979, and is the only one used as an effective oral therapy for *Candida* [2]. Itraconazole, fluconazole and more recently, posaconazole, voriconazole and isavuconazole, are the antimycotic drugs most widely used for systemic mycosis, while newer azoles, voriconazole and posaconazole seem to be effective in patients with fluconazole-resistant candida infection and to treat aspergillosis [3].

Furthermore, fluconazole and voriconazole have the best cerebrospinal fluid penetration, each resulting in concentrations of at least 50% of those in serum. This is important because fungal infections of the central nervous system are associated with high morbidity and mortality rates and are difficult to treat adequately [4, 5]. Fluconazole and voriconazole are quickly absorbed, showing a higher bioavailability through the oral route than itraconazole and posaconazole [4]. Anyway, triazoles are essential drugs in immune-compromised patients because of increased susceptibility to fungal infections [6]

All azole antifungals undergo some degree of hepatic metabolism, although for fluconazole, the drug elimination role is minimal, whereas this is not the case with itraconazole, voriconazole, and posaconazole, which are highly dependent on the liver metabolism for their elimination. For this reason, the most frequently reported adverse events attributed to the triazole drugs are hepatic toxicities [7].

Hypersensitivity reactions caused by systemic antifungal azole drugs are rarely reported in clinical practice, considering their widespread use, but unfortunately, when these occur, they have a major influence on the therapeutic approach in critically ill patients.

The most frequently reported hypersensitivity reactions to antimycotic azoles are allergic contact dermatitis forms, due to their widespread topical use [8, 9], but systemic hypersensitivity reactions have also been reported.

2. MATERIALS & METHODS

The English and French-language literature during a 34-year period (January 1, 1984 through July 31, 2019) was reviewed for reported immediate-type hypersensitivity reactions and delayed-type hypersensitivity reactions" caused by antifungal azoles.

The search was conducted using the PubMed database and Google Scholar. Search terms as "urticaria, angioedema, anaphylaxis" AND "dermatitis, fixed drug eruption, cutaneous adverse reactions, acute generalized exanthematous pustulosis, Steven-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia" AND "ketoconazole, itraconazole, fluconazole, posaconazole, voriconazole, isavuconazole, triazoles, azoles, antifungal", limited to French, and English were. Patients included were those who developed skin reactions after a known antifungal azole administration. Patients were excluded if they developed a toxic reaction only.

3. CLINICAL ASPECTS OF AZOLE ANTIFUNGAL HYPERSENSITIVITY

According to the World Allergy Organization (WAO), hypersensitivity reactions to drugs may be distinguished as immediate-type reactions, occurring within 1hr following drug administration, and delayed-type, appearing after 1 hour, usually within 48-72hrs, from drug intake. The timing of the appearance is related to the involvement of different immunologic pathomechanisms, the signs and symptoms of immediate reactions being directly attributable to the vasoactive mediators released by mast cells and basophils. The immunological mechanisms involved in this type of reaction are usually IgE-mediated. The most common symptoms are urticaria, pruritus, flushing, angio-edema, wheezing, gastrointestinal symptoms and even anaphylactic shock [10].

The immunological mechanism involved in the delayed-type reaction is a T cell response, also known as type IV reaction, although in fact, Ventura *et al*. [11] identified 4 subtypes of T cell-mediated hypersensitivity, subdividing type IV reactions into types IVa, IVb, IVc and IVd according to the subset of activated T cells involved and the inflammatory cytokines produced and released during the reaction, as shown in Scheme **1**.

3.1. Immediate-Type-Reactions

Although ketoconazole was the first agent to be used orally, few case reports of immediate-type hypersensitivity reactions, such as urticaria-angioedema [12, 13] or anaphylaxis [14], have been described in the literature. Diagnosis is not easy because such reactions are usually caused by food or other hidden allergens [15]. Only one case report of itraconazole-induced anaphylaxis is present in the literature [16] and two cases of urticaria angioedema [17, 18]. Despite its widespread use, even for fluconazole, there are only a few case reports of anaphylaxis [19-21], one case of angioedema [22] and even a Kounis syndrome, of coronary ischemia occurring during an immediate-type hypersensitivity reaction [23]. Such reactions were presumed to be IgE-mediated [16, 19], but no specific IgE to fluconazole has been isolated *in vitro*. As far as new triazoles are concerned, probably due to their less extensive use owing to their high costs, just two episodes of angioedema [24, 25] and anaphylaxis [26] induced by voriconazole have been reported in the literature. A retrospective study of the French Pharmacovigilance Database reported 227 cases of voriconazole-induced adverse reactions, observed over a period of 4 years, from January 1, 2002 to December 31, 2005 [27]. Among them, 39 cases (17 % of a total 227) reported cutaneous involvement with erythema (38% of skin reactions), maculopapular exanthema (17%), urticaria (13%), bullous eruptions (9%), blisters (6%), and purpura (4%). Phototoxicity was the most common skin adverse effect in 15 patients (43%), with erythema (43% of photosensitivity reactions), bullous eruptions (22%), eczema (5%), desquamation (10%), necrosis (5%), and cheilitis (5%). However, in 67% of cases, voriconazole has been administered with other drugs that may potentially cause skin eruptions [20]. The study suggested that immediate-type reactions such as urticaria represent a minority of cases and no case of anaphylaxis was reported in that study [27].

No case report of immediate-type hypersensitivity involving posaconazole or isavuconazole has yet been reported, nor any close investigation with an allergy workup.

3.2. Delayed-Type Reactions

3.2.1. Fixed Drug Eruption

Fixed Drug Eruption (FDE) is a cutaneous reaction represented by one or more nummular, discoid or oval erythematous or lilac-violet hued patches, sometimes surmounted by a blister. FDE results from systemic exposure to a drug, usually taken orally. The initial eruption is often solitary and frequently located on the lip or on the genitalia area, whereas other common locations of the initial lesion are the hip, lower back or sacrum, proximal extremities and trunk.

These lesions, which develop over a period of hours, but may persist from days to weeks, fade slowly leaving a residual oval hyperpigmented area. Normally they resolve in this way after stopping the drug administration, but they may recur at the same site with re-exposure to the drug. Drugs causing FDE are usually those employed intermittently.

Several sub-types of FDE have been observed and described, based mainly on their clinical features and the distribution of the patches, such as: a) a pigmenting fixed drug eruption, b) a generalized or multiple fixed drug eruption, c) a linear fixed drug eruption, d) a wandering fixed drug eruption, e) a non-pigmenting fixed drug eruption, f) a bullous fixed drug eruption, g) an eczematous fixed drug eruption, and g) an urticarial fixed drug eruption [28, 29].

Although FDE has been described following oral ketoconazole [30], miconazole [31] and itraconazole [32], it is the oral fluconazole administration which has been more frequently associated with FDE [33-51], above all in female patients who take fluconazole for vaginal candidosis. Furthermore, fluconazole-induced FDE may display particular morphological aspects such as lesions resembling herpes-like vesicles of the lips [52-57] or multiple bullous lesions [57-59]. The onset of herpes-like lesions on the lips in female patients taking fluconazole should be considered pathognomonic for fluconazole hypersensitivity, although few cases have been reported in the literature.

3.2.2. Exanthema and Dermatitis

The use of systemic azole antifungals may induce a cutaneous rash with different morphological aspects. These include maculopapular exanthema with eosinophilia, which has been reported following the use of itraconazole [60-62], fluconazole [63] and ketoconazole [64, 65], but sometimes lesions may appear as purpuric dermatitis [66]. A cutaneous rash can be associated with systemic symptoms such as acute drug-induced hepatitis [67-69], which has been reported for

Type of Reaction	T-Cell Type	Cytokines	Possible effector Mechanism	Clinical Symptoms
IVa	Th1	IFN-g,TNF-a	Monocyte / macrophage activation	Contact dermatitis, bullous exanthema
IVb	Th2	IL-5, IL-4, IL-13, eotaxin	T-Cells with eosinophilic inflammation	Maculopapular and bullous exanthema
IVc	Cytotoxic T cells	Perforin, granzyme B	CD4+/CD8+ mediated T cell killing	Steven Johnson and Lyell syndrome (bullous exanthema)
IVd	T cells	CXCL-8 GM-CSF	T cell leading to recruitment and activation of neutrophils	Acute Generalized Exanthematous Pustulosis (AGEP)

Scheme 1. Revised type IV hypersensitivity reactions [8].

fluconazole [67, 68] and voriconazole [69], or fever onset during an erythematous maculopapular rash following fluconazole use [70,71].

Furthermore, the previous use of topical antifungal azoles may cause an under or misdiagnosed sensitization, then eliciting a generalized cutaneous reaction following systemic administration of an antifungal azole, which may induce an allergic cross-reactivity with the topical azoles. Hidden sensitization can be due to a topical application of an antifungal azole, eliciting a maculopapular eruption after systemic administration [72], or alternatively to exposure to a potentially cross-reactive antifungal azole, not only to treat a cutaneous mycosis in the patient, but even due to the use of veterinary products to treat a dermatophytes infection in patients' pets [73].

So, cross-sensitivity between topical and systemic azoles has been demonstrated for miconazole with ketoconazole [74], clotrimazole and croconazole with itraconazole [75] and clotrimazole with fluconazole [76]. Also sensitivity to imidazoles/nitroimidazoles in subjects sensitized to methylchloroisothiazolinone/methylisothiazolinone has been investigated [77].

A particular aspect of general allergic contact dermatitis is symmetrical drug-related intertriginous and flexural exanthema, now called the acronym SDRIFE and previously known as baboon syndrome, because it induces erythematous lesions of the buttocks.

Morphologically, SDRIFE is expressed as a sharply demarcated erythema of the buttocks and perianal zone or V-shaped erythema of the inguinal area and symmetrical involvement of the flexures, but it is not associated with any systemic symptoms [78].

Baboon syndrome/SDRIFE has been described following the use of ketoconazole [79], itraconazole [80] and fluconazole [81]. Yet, there is even the possibility that topical antifungals may cause a widespread skin reaction, going beyond the application area, and the reaction may appear as eczematous dermatitis in the case of isoconazole [82] or as an erythema multiforme-like eruption caused by topical tioconazole [83], although a genuine erythema multiforme following systemic assumption of itraconazole has also been described in the literature [84]. Systemic involvement due to topical application of azoles is more common than might be expected. Swiss dermatologists observed over a period of 4 years, from 2008 to 2011, ten patients with severe cutaneous eruptions caused by a topical formulation of associated corticosteroid, tixocortolpivalate and an antifungal azole medication, clotrimazole [85]. Patients developed widespread eczema, but also erythematous, maculopapular exanthema, erythema multiforme-like or blistering eruptions, that occurred from 7 to 21 days after beginning the topical therapy. They also evinced an intense eczematous reaction at the application sites, associated with peripheral blood eosinophilia. However, patch tests with clotrimazole resulted positive only in 4 patients [85].

3.2.3. Serious Cutaneous Adverse Reactions (SCARs)

Serious Cutaneous Adverse Reactions (SCARs) to drugs consist mainly of Steven-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), Acute Generalized ExanthematousPustulosis (AGEP) and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome.

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe mucocutaneous reactions, most commonly triggered by medications, and characterized by extensive necrosis and detachment of the epidermis with mucosal involvement in 90% of affected patients. SJS/TEN SJS is considered a disease continuum and the different forms are distinguished according to the severity of body surface involved with blisters and erosions (SJS inferior to 10%, TEN superior to 30% and overlap SJS/TEN between 10-30%). SJS/TEN is associated with fever, malaise, renal and liver impairment and skin detachment. SJS/TEN occurs more frequently in patients with an immune depressive status and related immune dysregulation like HIV infection, graft-vs-host disease, systemic lupus erythematosus, malignanciesof mostly hematologic type and mixed essential cryoglobulinemia, because of its immuno-mediated pathogenesis. A retrospective study by a group of Italian clinicians showed that among 35 patients with SJ/TEN, observed over 11 years in an Italian Burns Centre, 9 of them were cancer patients. Beta-lactam antibiotics and azole antimycotic fluconazole were the drugs most frequently associated to the serious skin reaction in onco-hematologic patients, while antiepileptics were more commonly the agents responsible for SJS/TEN in patients with brain tumors [86]. The first case report of SJS induced by fluconazole dates back to 1991 [87], and two years later, Spanish dermatologists described the first case of TEN triggered by fluconazole in an HIV-positive male patient [88]. Since then, other cases of SJS/TEN caused by fluconazole [89-95] and voriconazole [96-98], mainly in HIV-positive patients or oncologic subjects, have been reported. However, SJS/TEN induced by fluconazole may affect even immune-competent patients [89, 93]. For that reason, Paszmatzi *et al*. have speculated that, while in HIV-positive individuals, long-term high doses of fluconazole are more likely to trigger serious cutaneous reactions, short-term low, intermittent dosages of fluconazole seem to be more responsible for inducing SJS/TEN in non-immunocompromised patients [93].

Sometimes SCARs may present atypical features with borderline aspects between a fixed drug eruption and SJS/TEN [99] or a photo-induced SJS/TEN, which is a particular variant of that disease, in which bullae and erosions appear only in photo exposed areas [100]. In that case, itraconazole was the culprit drug [100]. Interestingly, photodermatitis induced by itraconazole [101] and mainly by voriconazole [102-104], is reputed to be phototoxic reaction and not photoallergic because when photo patch tests were carried out [101], they resulted negative. However, because only photo patch tests can discriminate between phototoxicity or photoallergy and these tests are not easy to perform *in vivo* routinely, the real incidence of allergic photodermatitis to systemic triazoles could be underestimated.

Lastly, another cutaneous hypersensitivity syndrome triggered by systemic triazoles is Acute Generalized Exanthematous Pustulosis (AGEP). It is characterized by aseptic disseminated cutaneous pustules associated with fever, malaise and peripheral blood leucocytosis. Ketaconazole [105],

itraconazole [106-108] and fluconazole [109-111] have been reported to cause AGEP.

Only one recent case of atypical DRESS syndrome with no eosinophilia and agranulocytosis has been reported in the literature, following voriconazole administration in a 48-year-old Japanese woman taking the drug for pulmonary aspergillosis [112].

Suggestively, in all the aforementioned case reports of FDE, mild dermatitis and SCARs, the adverse cutaneous reaction was always associated with the oral intake of triazoles, including the second generation antifungal voriconazole [97, 98], where the reaction occurred when the drug was switched from intravenous to the oral route [91]. In a single case, a patient developed a rash and hepatitis but tolerated voriconazole when it was administered through the intravenous route [69]. Rarely, fluconazole induced a cutaneous rash when given intravenously [70]. However, in a French post-marketing retrospective study on voriconazole adverse reactions, among 39 patients who developed cutaneous hypersensitivity reactions, voriconazole was administered intravenously to 14 cases [27]. Even immediate-type reactions are rarely associated with the intravenous administration of triazole molecules [16, 26].

4. ALLERGIC CROSS-REACTIVITY AMONG ANTIFUNGAL AZOLES

Because azoles drugs include a large family of substances with an imidazole ring in their chemical structure, as shown in Table **2**, it is not surprising that sometimes allergic cross-reactivity may involve compounds other than antifungals, and patients who are allergic to anti protozoic drugs may evince allergic reactions to some antimycotics, too [113]. Patch tests with specific series are required [114].

In immediate-type reactions, which are presumably supported by a specific IgE to the single antimycotic molecule, no allergic cross-reactivity has been evidenced between ketoconazole and fluconazole in skin tests [10], and challenge test evidenced no cross-sensitivity between oral itraconazole and intravenous voriconazole [16] or between itraconazole and ketoconazole or fluconazole at an oral challenge test [17]. The few case reports of immediate-type reactions involving fluconazole date back to the 90's, when no other triazole drugs such as voriconazole or posaconazole were available. In the same way, no cross-sensitivity among antifungal ketoconazole and proton pumps inhibitors or other azoles was revealed, when investigated [10, 115]. Lastly, isavuconazole was tolerated in a 48-year-old female patient with angioedema induced by voriconazole and administered in a graded challenge protocol [25].

On the contrary, in cases of T-cell-mediated reactions, the existence of cross-reactivity among the different imidazole compounds has been investigated and demonstrated by different authors.

Due to their widespread use as topical medications, antifungal azoles may induce allergic contact dermatitis, so many researchers used patch tests to explore the potential patterns of cross-reactivity among azoles antifungal drugs.

In 1988, Motley and Reynolds firstly proposed a cross-reactive pattern involving 2-4 dichlorophenylethylimidazoles, based on substitution of a phenyl ring close to the imidazoles structure [116].

Later, Baes reported a pattern of cross-reactivity among antifungal azoles, namely beta-substituted-1-phenylethylimodazole with an ortho-chlorine substitution, suggesting that such an ortho-chloro substitution on the phenyl or thienyl ring was the immunologic site influencing cross-reactivity among topical azoles [117]. The ortho-chloro group includes isoconazole, croconazole, tioconazole, miconazole and oxiconazole and cross-reactivity between croconazole and itraconazole was evidenced in the patch tests [75], but itraconazole is the only triazole with chlorine atoms in its chemical structure, that has been substituted by fluorine atoms in the other systemic triazoles.

Moreover, Goossens *et al*. reviewed the literature and added their experience with 15 cases of imidazole contact dermatitis, paying particular attention to cross-reaction patterns. They were able to identify three common patterns of cross-reactivity: isoconazole, miconazole and econazole were linked, as were sertaconazole, miconazole and econazole. The third link was isoconazole and tioconazole, although they suggested that even cross-reactivities are unpredictable [9] and, in their opinion, ketoconazole seemed to be

Table 2. Imidazoles Drugs.

Antifungals:
Phenethyl Imidazoles: Ketoconazole, miconazole, tioconazole, isoconazole, enilconazole, econazole, sulconazole, sertaconazole and oxiconazole
Phenmethyl Imidazoles: Clotrimazole, croconazole and bifonazole
Triazoles: Fluconazole, itraconazole, posaconazole, voriconazole and isavuconazole (systemic use) and eficonazole (topical use)
Antiprotozoal Agents: Metronidazole, tinidazole, secnidazole and benznidazole
Anti-Helmintic Agents: Albendazole, mebendazole and thiabendazole
Antihistamine2: Cimetidine
Proton Pump Inhibitors: Lansoprazole, omeprazole, rabeprazole and esomeprazole
Antiplatelet: Ticagrelor

more similar to the triazoles structure, except for the imidazole ring, although cross-reactivity between ketoconazole and miconazole has been reported [74].

Therefore, it has been suggested that azoles belonging to phenyl ethyl imidazoles are more likely to cross-react among themselves than with phenylmethylimidazoles, which show a low degree of cross-sensitivity among themselves [118], but these are not well-established rules.

Because topical imidazoles use may be an undervalued route of sensitization to systemic triazoles, it is likely that most of the hypersensitivity reactions to triazoles are T cell-mediated, as confirmed by clinical experiences. Thus, the aforementioned classifications of imidazole cross-sensitivity for contact dermatitis could be used in systemic delayed-type hypersensitivity caused by triazoles. Nevertheless, in cases of systemic triazoles, it is possible that liver cytochrome P450 isoforms metabolic pathways may change the immunogenicity of triazole molecules, as shown for itraconazole, generating various metabolites such as hydroxyitraconazole, keto-itraconazole, N-desalkyl-itraconazole [119]; that could make it more difficult to foresee cross-reactive phenomenons.

In light of the experiences described in the literature, it is difficult to establish which epitope is recognized by T cells in antifungal azoles for systemic use.

For instance, Gupta and Thami first described a cross-sensitivity between fluconazole and itraconazole, but not to ketoconazole, in a 52-year old woman with FDE induced by fluconazole. The patient underwent oral graded challenge with fluconazole, itraconazole and ketoconazole every 4 weeks. A flare-up of the lesions was observed with fluconazole 25mg and itraconazole 25mg, but not with ketoconazole up to 200mg, that failed to reactivate lesions, so the authors postulated that the epitope recognized by T cells was the common azole ring. In their case report, the introduction of the third nitrogen atom in the triazole ring was sufficient to change the immunogenicity with the imidazole [39], but in many case reports, patients with FDE induced by fluconazole tolerated oral itraconazole [41, 45, 46, 49, 51, 56] in the challenge test.

On the other hand, in a 65-year-old patient with contact dermatitis to luliconazole, Tanaka *et al*. elicited a positive patch test to lanoconazole, but not to neticonazole. All three compounds belong to the class of vinyl-imidazoles, but only luliconazole and lanoconazole presented the same dithioacetal moiety, which was probably recognized by T-cells [120]. Umebayashi and Ito, on the contrary, observed a patient with contact dermatitis to lanoconazole who developed cross-sensitivity to netilconazole following four-months use after the first diagnosis, and attributed the imidazole cross-reactivity to their common vinyl group [121].

Yet, in another case of FDE induced by ornidazole, an anti protozoic imidazole agent in a 42-year-old woman, the patient evinced cross-reactivity to fluconazole, too, but she tolerated oral metronidazole, itraconazole and ketoconazole and topical isoconazole. On that basis, the authors suggested that since propan-2-ol is the common chemical group of both molecules, it was responsible for a cross-reaction between ornidazole and fluconazole [122].

Previously, in another FDE, it has been suggested that the propanol side chain could be the epitope causing cross-sensitivity between ornidazole and secnidazole, another anti-protozoal drug [123].

In other cases of FDE, cross-reactivity between metronidazole and ketaconazole and between fluconazole and tinidazole has also been described [113, 114]. Farbre *et al*. observed the rapid onset of AGEP following the third day of therapy with fluconazole 200mg daily in a 65-year-old female patient previously treated with econazole powder [111]. The authors could not perform any diagnostic patch test because of the patient's compromised neurological status, but the topical application of econazole following the AGEP resolution resulted in a flare-up of pustular lesions, suggesting that econazole induced the hypersensitivity, and there was an immunologic cross-reactivity between econazole and fluconazole [111].

Probably, the aromatic ring in imidazoles and triazoles is an important epitope for T-cells recognition, causing cross-reactivity, but that is not the only epitope in azole molecules, and this is what makes imidazoles cross-reactivity unpredictable.

Furthermore, a potential cross-reactivity among azoles and some preservatives commonly used in cosmetics, such as thiazolinone derivatives, i.e. Methylisothiazolinone (MI), Methylchloroisothiazolinone (MCI), Benzisothiazolinone (BIT), and Octylisothiazolinone, has been suggested [124].

These preservatives are present in cosmetics, but also in household detergents, water-based paints and other liquids for industrial purposes [124].

Thiazolinone compounds show an aromatic ring where a nitrogen atom is substituted by a sulphur atom, although such a cross-sensitivity with azoles has been considered doubtful in a few case reports [82, 125].

Recently, Stingeni *et al*. enrolled 149 patients (35 men and 114 women; mean age 40.0 y.o.) with a recent diagnosis of contact sensitization to MCI/MI revealed by 0.02% aqueous patch tests [126]. Patients were investigated through patch tests with phenethyl imidazoles (econazole nitrate, fenticonazole nitrate, isoconazole nitrate, ketoconazole miconazole nitrate, sertaconazole nitrate, and tioconazole) and phenmethyl imidazoles (bifonazole nitrate and clotrimazole), all at 2% pet., and anti-parasite agents as nitroimidazoles, (metronidazole and tinidazole, albendazole and mebendazole), all at 5% pet.

They identified 9 patients (6.0%) who reacted to at least one of the patch-tested imidazoles and nitroimidazoles, particularly, all nine patients reacted to imidazoles: eight to phenethyl imidazoles (5.3%) (tioconazole, 3; ketoconazole,2; isoconazole,1; miconazole,1; sertaconazole,1), and one reacted to a phenmethyl imidazole (0.7%) (clotrimazole), although, interistingly some patients had never used topical azoles previously. Furthermore, authors performed a computerized conformational analysis to investigate the spatial electron cloud geometries of MCI, MI and the imidazoles/nitroimidazoles that elicited positive reactions in patch tests [126].

Such a computerized conformational analysis of the different molecular structures seemed to confirm that the electronic shapes and the distributions of positive and negative ions in the chemical structures of MCI and MI were similar to those of isoconazole, miconazole, sertaconazole, and tioconazole. It was particularly evident that isoconazole, sertaconazole and tioconazole showed a spatial electron cloud geometry similar to that of MI, whereas miconazole showed the same spatial electron cloud geometry as MCI.

For that reason, authors suggested that cross-reacting molecules are characterized not only by similar sizes or shared reactive chemical groups but also by similar spatial geometries and electron cloud distributions [126]

Due to the complexity of their chemical structure, azole antifungal drugs show a great variety of epitopes, so it is possible that T cells may recognize the whole molecule, the azole/trazole ring or the side chain. As far as chlorine or fluorine atoms are concerned, they could influence the potential pattern of cross-reactivity as halogen atoms due to their electron-attraction effect, stabilizing the molecule, as evidenced in halogenated corticosteroids [127].

The possibility that similar electronic distributions may influence the crossreactivity of azoles, not only when compared with MCI/MI, but among different azole molecules, contributes to make the identification of cross-reactive patterns more elusive.

In cases of systemic administration, the absence of cross-reactivity between fluconazole and voriconazole has been demonstrated using a graded challenge test, introducing voriconazole gradually in a patient with a previous reaction to fluconazole [68], and confirmed in another case report [128]. Although itraconazole may be tolerated in patients with fluconazole-induced FDE [45, 49, 51, 53] and with exanthema induced by fluconazole [63, 128], there are reports demonstrating the existence of cross-sensitivity between these two triazoles in generalized dermatitis [129, 130]. Of course, given the potential hazard, cross-reactivity was not investigated in patients with SCARs and amphotericin B was introduced as needed.

5. DIAGNOSTIC PROCEDURES AND MANAGEMENT OF TRIAZOLE HYPERSENSITIVITY

The diagnostic accuracy of skin tests for antifungal azoles is not well established. In immediate-type reactions, skin prick tests resulted positive to ketoconazole [12], fluconazole [19] and voriconazole mg/ml, diluted 1/10 in an anaphylactic reaction [26], whereas when skin prick tests were performed for itraconazole, it resulted negative. Although fluconazole has been available in the market since 1990, most of the authors reported that they had not carried out skin tests with fluconazole because they did not know its negative or positive predictive value. At immediate reading, intradermal tests with fluconazole have been reported positive in a single case [23] with the diluted molecules, 2mg/ml at 1/10, 1/100 and 1/1000.

In delayed-type reactions, patch tests [114] showed a high rate of false-negative results. Although many authors used petrolatum as vehicle for patch testing imidazoles, Raulin and Frosch compared petrolatum, ethanol and methyl ethyl ketone and found more false-negative reactions with petrolatum than other vehicles [8]. However, patch test has been successfully used to confirm the AGEP diagnosis and sensitization [112]. Intradermal test with delayed reading can be useful in maculopapular exanthema [59], whereas patch test or topical open provocation test with fluconazole 10% in petrolatum applied on previous FDE lesions elicited a positive response in a few cases, including a flare-up of FDE [34, 47].

Even a laboratory test like skin biopsy is a helpful tool to confirm the diagnosis, while the Lymphocyte Transformation Test (LTT) seems to be a promising tool, not only to confirm the diagnosis [107], but also to investigate potential cross-sensitivities among azoles [50], although it cannot be considered an easily performed routine test. The most reliable test at present is a challenge test with the suspected molecule, but it cannot be performed in patients with SCARs.

Because the polyene derivative nystatin and echinocandins are active mainly against yeasts, *Candida* species, azoles, triazoles and amphotericin B show a broad spectrum of activities against dermatophytes, yeasts and moulds [131], so azole antifungals remain fundamental drugs to treat systemic fungal infections. Drug desensitization and a graded challenge test with another triazole are the strategies followed to avoid using amphotericin B in view of its toxicity. Bittleman firstly used a desensitization protocol to itraconazole in 1994 in a pruritic rash, as illustrated in Table **3** [59] and their protocol was replicated in a patient with fungal sinusitis [132].

Table 3. Itraconazole Desensitization Schedule Through an Oral Increasing Doses of Itraconazole and an Interval between Doses 30 Minutes.

Dose*	(mg)t
1	1
2	2
3	4
4	8
5	16
6	32
7	64
8	128
9	200

*The itraconazole capsules were crushed; and the contents ofthe capsule were weighed, mixed in applesauce, and given to the patient.

One year later, Craig *et al*. performed the first desensitization to fluconazole in an HIV male patient, as shown in Table **4** [129].

The same protocol was modified by Takahashi *et al*. who gave 4, 10, 20, 50, 100 and 200 mg daily, reaching the therapeutic dose in 7 days instead of 15 [66]. Jariwala *et al*. shortened the desensitization procedure to 5 days only, as shown

Table 4. Slow Procedure for Fluconazole Oral Desensitization.

Day	Concentration	Dose	Total mg
1	1mg/ml	0.2ml	0.2
2	1mg/ml	0.4ml	0.4
3	1mg/ml	0.8ml	0.8
4	1mg/ml	1.6ml	1.6
5	1mg/ml	3.2ml	3.2
6	1mg/ml	6.4ml	6.4
7	10mg/ml	1.0ml	10
8	10mg/ml	2.0ml	20
9	10mg/ml	4.0ml	40
10	50mg tablet	1	50
11	50mg tablet	2	100
12	50mg tablet	3	150
13	200mg tablet	1	200
14	100mg tablet	3	300
15	200mg tablet	2	400

Continue 400mg each day without stopping.

Table 5. Accelerated Desensitization Protocol with Oral Fluconazole.

Hour	Concentration, mg/mL	Volume Administered	Dose Administered
0	2	1mL	2mg
6	2	1mL	2mg
12	2	2mL	4mg
18	2	4mL	8mg
24	2	8mL	16mg
30	2	15mL	30mg
36	2	30mL	60mg
42	2	60mL	120mg
48	NA	NA	200mg (tablet)
60	NA	NA	200mg (tablet)

A premedication with diphenhydramine, 25mg, and famotidine, 20mg, 30 minutes before the first dose. Continue the diphenhydramine, 25mg, 3 times daily and famotidine, 20mg, twice daily during the entire desensitization. Abbreviation: NA, Not Applicable).

in Table **5** [71]. Apart from slow desensitization protocols for fluconazole, even rapid [21] and semi-rapid desensitization schedules as in Table **6** [130] have been developed to rapidly reach the therapeutic dose in an HIV patient with active pulmonary fungal infections.

Interestingly, treatment with fluconazole caused an immediate-type reaction leading to a cutaneous macular rash in a patient, after the fifth desensitization process, suggesting a switch from an immediate-type to a delayed-type hypersensitivity [21].

Jean and Kwuong performed a successful rapid desensitization procedure to voriconazole in a 13-year old boy [26], this being the only intravenous desensitization protocol to triazoles described in literature, whereas all the others were

Table 6. Fast Desensitization Procedure.

Step	Concentration mg/mL	Volume mL	Dose Administered mg	Cumulative Dose mg
1	0.02	1	0.02	0.02
2	0.02	2	0.04	0.06
3	0.02	4	0.08	0.14
4	0.2	0.8	0.16	0.30
5	0.2	1.6	0.32	0.62
6	0.2	3.2	0.64	1.26
7	2	0.75	1.50	2.76
8	2	1.5	3.00	5.76
9	2	3	6.0	11.76
10	20	0.6	12	23.76
11	20	1.2	24	47.76
12	20	2.5	50	97.76
13	20	5.0	100	197.76

The procedure is given for rapid desensitization of fluconazole, 0.02mg/mL. There was a 15-minute interval between doses. The patient was observed for 2 hours without event.

Table 7. Voriconazole Intravenous Desensitization Protocol.

Dose	Concentration (mg/mL)	Dose (mg)	Cumulative Dose (mg)	Time (min)
1	0.1	0.02	0.02	15
2	0.1	0.05	0.07	30
3	0.1	0.1	0.17	45
4	1 0.	25	0.42	60
5	1	0.5	0.92	75
6	1	1	1.92	90
7	5	2	3.92	105
8	5	4	7.92	120
9	5	8	15.92	135
10	5	16	31.92	150
11	5	32	63.92	165
12	5	64	128.92	180
13	5	128	255.92*	195
14	5	207	335†	210

*Maintenance dose is 4mg/kg every 12h, approximately 223mg.
†Loading dose is 6mg/kg, approximately 335mg.
Table 7a. Graded challenge with oral voriconazole:
-starting at a dose of 25mg daily on day 1,
75mg b.i.d. on day 2,
150mg b.i.d. on day 3,
300mg daily on day 4,
and then 200mg b.i.d. thereafter.

given by oral route. Morales *et al*. preferred to desensitize a patient with angioedema due to voriconazole using isavuconazole, probably due to the unknown pattern of triazole cross-reactivity [25]. In their experience, Oriel *et al*. suggested that in patients with mild delayed-type cutaneous hypersensitivity, even rapid desensitization protocols may work [133]. Graded challenge test and desensitization protocols with voriconazole are reported in Tables **7** and **8**. Lastly, a

Table 8. Oral Voriconazole IDT Protocol (117).

0.4mg/mL Oral Suspension Voriconazole				
Dose	**Volume (mL)**	**Dose (mg)**	**Cumulative Dose (mg)**	**Time (min)**
1	0.25	0.1	0.1	30
2	0.5	0.2	0.3	60
3	1	0.4	0.7	90
4	1.5	0.6	1.3	120
5	2.75	1.1	2.4	150
6	4	1.6	4	180
TOTAL VOLUME = 10mL				
40mg/mL Oral Suspension Voriconazole				
Dose	**Volume (mL)**	**Dose (mg)**	**Cumulative Dose (mg)**	**Time (min)**
7	0.08	3.2	7.2	210
8	0.16	6.4	13.6	240
9	0.31	12.4	26	270
10	0.5	20	46	300
11	0.61	24.4	70.4	330
12	1.24	49.6	120	360
TOTAL VOLUME = 2.9mL				

Table 9. Isavuconazole 1 Graded Dose Challenge.

Day	Dosage, Route, and Frequency	Ratio of dose Administered to Recommended Adult Dose
1	3.72mg in 250mL normal saline IV once	1:100
2	37.2mg in 250mL normal saline IV once	1:10
3	186mg PO once	1:2
4	372mg PO once	1:1
5	372mg PO every 8 hours	Usual loading dose

1 After administration as isavuconazonium sulfate via 372mg vials or 186 mg capsules, the drug undergoes metabolism to the active form of isavuconazole at the equivalent of 200mg (per 372mg vial) or 100mg (per 186mg capsule).
2 To prepare, reconstitute 372mg (1 vial) with 5mL SWFI (sterile water for injection). Then add to 250mL normal saline bag (Bag A). For the final dose, take 2.5mL of Bag A and add to 250mL normal saline bag (Ba).

graded challenge test with isavuconazole was started intravenously and switched to an oral formulation of isavuconazium (Table **9**).

Although there are some differences between a graded challenge test and a desensitization procedure, because a graded challenge test involves fewer steps and may be performed with alternative molecules, some authors consider such methods very similar [134].

CONCLUSION

Despite their widespread use [2,6], triazoles seem to induce rare cutaneous hypersensitivity reactions, but the pathomechanisms, risk factors, diagnostic and management strategies, including skin tests and challenge tests, are little known and poorly investigated. Probably the severity of the diseases and the compromised clinical conditions of patients, as for instance, in patients affected by hematologic malignancies, discourage medics to perform skin tests or laboratory tests which could be seen as an unuseful diagnostic doggedness by the patient and other doctors.

CURRENT & FUTURE DEVELOPMENTS

Because of the widespread use of azole antifungal agents, also in immune-compromised patients, further, more in-depth investigations of hypersensitivity to triazoles are poorly warranted.

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CONFLICT OF INTEREST

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