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Research Article

A REVIEW ON: HISTORY, PHARMACOLOGICAL POTENTIAL OF MEDICINALLY IMPORTANT ANTIFUNGAL AZOLE DERIVATIVE

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A B S T R A C T

Fungal infections in critically ill or immune suppressed patients were increasing in incidence in the human population over the last 1-2 decades. There were few advances in antifungal therapy until recently; there were few choices from which to select a treatment for systemic mycoses. While, in the past decade, there have been several developments in this area. Antifungal agents are sufficiently diverse in activity, toxicity and drug interaction potential. Azoles are synthetic and semi-synthetic compounds. They have an extensive spectrum of activity. Triazole antifungal is active to treat an array of fungal pathogens, whereas imidazoles are used almost exclusively in the treatment of superficial mycoses and vaginal candidacies. In spite of the advances, serious fungal infections remain difficult to treat and resistance to the available drugs is emerging. Use of the now accessible azoles in combination with other antifungal agents with different mechanisms of action is likely to provide enhanced efficacy. The present review aims to explore the pharmacology, pharmacokinetics, spectrum of activity, safety, toxicity and potential for drug–drug interactions of the azole antifungal agents.

INTRODUCTION

Fungi are common pathogens in critically ill or immune suppressed patients. Fungal infections (mycoses), though not as frequent as bacterial or viral infections, have nevertheless been increasing in frequency in the human population over the last 1-2 decades. In addition, a number of fungal infections can be tricky to treat, even when the offending organisms identified and suitable therapy is applied. Fungi have exclusive characteristics, distinct from their mammalian hosts, allowing for selective targeting of therapeutic drugs. Fungi are much more complex organisms in comparison to bacteria, are in fact eukaryotic and often grow fairly slowly. So, only a few drugs are aimed at interfering with cell division and have limited use. Though, in the past decade, there have been several developments in advances in antifungal therapy to select a treatment for systemic mycoses. A new class of antifungal agents has been developed, safer and/or more bioavailable formulations of itraconazole and amphotericin B have been marketed, and another compound voriconazole has been added to the triazole class of agents. Antifungal agents are sufficiently diverse activity, toxicity and drug interaction potential to allow clinicians to distinguish among agents based upon these characteristics when tailoring therapy to meet the needs of a particular patient. The present review focuses on the pharmacology, pharmacokinetics, safety and potential for drug-drug interactions of antifungal agents.[1]

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There are more than 1,00,000 different species of fungi; many of which are useful, but few hundreds are pathogens. Fewer than 20 species of fungi causes greater than 90% of all human mycotic infections. Pathogenic fungi affecting human is eukaryotes, generally existing as filamentous molds or intracellular yeasts.

Fungal organisms are characterized by a low invasiveness and virulence. Factors that contribute to fungal infections include necrotic tissue, a moist environment and immunosuppressant. Fungal infections can be primarily superficial and irritating or systemic and life threatening. Dimorphic fungi, which grow in the host as a yeast-like form but as molds in vitro at room temperature, include Coccidioides immitis, Histoplasma and Rhinosporidium, which grow inside host cells. Topical infections caused by fungi may become established on the skin and nexa or mucous membranes (buccal, vaginal).[2] The external auditory canal and cornea may also be invaded by yeasts and fungi that are opportunistic pathogens. Systemic mycoses are infections with fungal organisms that exist in the environment, enter the host from a single portal of entry and disseminate within the host usually to multiple organ systems. The soil reservoir is the primary source of most infections, which can be acquired by inhalation, ingestion or traumatic introduction of fungal elements.[2]

The azoles are therapeutically useful antifungal agents with wide spectra against yeasts and filamentous fungi responsible for either superficial infection. Clotrimazole, miconazole, ketoconazole, econazole, itraconazole, fluconazole and

voriconazole are the most clinically important members of this group.[2]

History of Antifungal Azoles

The 1st report of antifungal activity of an azole compound, benzimidazole was in 1944 by Woolley[3], who was studying biotin deficiency in animals and microbes. He noted the structural similarity of biotin and purines to benzimidazole, but the biological effects of benzimidazole were not reversed by biotin, whereas they were reversed by the purines adenine and guanine. Since mycotic diseases were of minimal interest in 1944. Woolley's initial discovery was largely ignored, although his data were confirmed in 1949. 30 years later, Vanden Bossche observed that phenethylimidazole, another azole moiety with antifungal activity, inhibited the uptake of purines in yeast form Candida spp. by interference at the cell membrane. In 1952, Jerchel *et al*. [3] revived Woolley's work and reported that certain substituted benzimidazole compounds had significant antifungal activity. This publication encouraged other investigators to screen this group of chemicals in search of a clinically useful antifungal agent. The come through came in 1958 to 1959 when chlormidazole, a chlorobenzyl imidazoles, was developed and studied in clinical trials.[3] Chlormidazole was sold as a 5% topical cream, the first azole derivative developed and marketed as an antifungal drug. With the introduction of chlormidazole, interest in the antifungal activity of azole compounds began to increase. For example, after the introduction of thiabendazole, a thiazolyl-benzimidazole, in 1961 by Merck Sharp & Dohme for use as a broad-spectrum anthelmintic drug, Robinson *et al*.[3] tested the compound for antifungal activity in vitro. It was efficient against many dermatophytes and Aspergillus species, but since its activity against yeast-like fungi was minimal, the compound was not developed as an antifungal agent. Similarly, mebendazole, a benzoyl-benzimidazole developed by Janssen Pharmaceutica (Beerse, Belgium) in 1973 as a broad-spectrum anthelmintic agent, was shown to have antifungal activity.[3] In spite of the fact that the antifungal activity of these two compounds was not pursued; the data supported the concept that two azole compounds had potential as antifungal drugs for human use. In the late 1960s, three compounds from two different laboratories were introduced in the literature; these drugs firmly established azoles as antifungal agents.

Clotrimazole, developed by Bayer AG (Wuppertal, Federal Republic of Germany), and miconazole and econazole, developed by Janssen Pharmaceutica, were introduced within months of each other. This era of azole antifungal compounds was so new and competitive that the less descriptive report of clotrimazole antifungal activity was published 3 years prior to the more detailed description of the chemical synthesis. These three imidazoles continue to be used today for treatment of fungal infections, demonstrating the success of these early discoveries. Unhappily, their use also reveals the slow evolution of the azole class of antifungal drugs during the past two decades. Though progress with this group of antifungal agents has been slow, several clinically useful compounds have been developed, and many, which appear promising, are presently under development and clinical evaluation. A few imidazoles compounds (ketoconazole, in particular) represent major advances in antifungal chemotherapy. New triazole derivatives e.g. fluconazole and itraconazole, appear to be less toxic and more active than ketoconazole. These and several other antifungal azole derivatives are discussed in this review.

Classification of Anti-Fungal Agents

Table 1 Classification of Anti-Fungal Agents

Class	Route of administration	Examples
Imidazole Group	Topical agents	Clotrimazole, Miconazole, Butaconazole, Econazole
	Systematic agents	Ketoconazole
Triazole Group	Topical agents	Itraconazole, Teraconazole
	Systematic agents	Itraconazole, Fluconazole, Voriconazole

Antifungal Activity

Mode of Action

Imidazole drugs apply their antifungal effects through alteration of the cell membrane permeability of susceptible yeasts and fungi by blocking the synthesis of ergosterol (demethylation of lanosterol is inhibited), the primary cell sterol of fungi.[4] In addition, other enzyme systems are also impaired, like those required for fatty acid synthesis. More, imidazole drugs induce changes of oxidative and per oxidative enzyme activities; toxic concentrations of hydrogen peroxide develop intracellularly. The overall effect is cell membrane and internal organelle disruption and cell death.

Triazole drugs like as imidazole ones, exert its antifungal effect by dose-dependent inhibition of CYP-dependent 14α-demethylase, which is necessary for the translation of lanosterol to ergosterol which ergosterol is important for the stability of the fungal cell membrane and inhibition of its biosynthesis compromises cell membrane integrity Triazole drugs also secondarily target other steps in the ergosterol biosynthesis pathway. For example, in fluconazole-susceptible C. albicans fluconazole only partially inhibits ergosterol and completely blocks obtusifoliol synthesis, whereas voriconazole completely inhibits both ergosterol and obtusifoliol synthesis. Itraconazole and fluconazole may also inhibit 3- ketoreductase, which catalyzes the reduction of the 3-ketosteroid obtusifolione to obtusifoliol in C. neoformans.[4]

Classifications of Azoles

The azoles are classes of five-membered nitrogen heterocyclic ring compounds that contain at least one other non-carbon atom of nitrogen, sulfur, or oxygen [5], as showed in fig. 1. The parent compounds are aromatic and have two double bonds with fewer one and only one ion pair of electron from each heteroatom in the ring . The numbering of ring atoms in azoles starts with the heteroatom that is not part of a double bond, and then proceeds towards the other heteroatom.[5] Azoles are groups of fungistatic agents with wide-spectrum activity. They are classified into two groups: imidazoles and triazoles. The members of each group are structurally related and alterations in side-chain structure determine the antifungal activity as well as the degree of toxicity. Clotrimazole, miconazole (base or nitrate salt), ketoconazole, econazole (base or nitrate salt), butaconazole, teraconazole, voriconazole, itraconazole, and fluconazole are the most clinically important members of this group.[5]

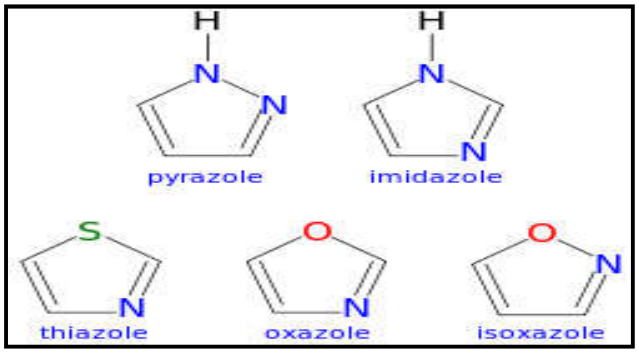

Figure 1 Classification of Azoles

Pharmacology of Azoles

Mechanism of Action

The systemically acting azoles include fluconazole, itraconazole, ketoconazole, posaconazole, and voriconazole. The azoles use a fungistatic effect by dose-dependent inhibition of CYP-dependent 14α-demethylase, which is necessary for the conversion of lanosterol to ergosterol. Ergosterol is important for the stability of the fungal cell membrane and inhibition of its synthesis compromises cell membrane integrity.[6]

The triazoles also secondarily target other steps in the ergosterol biosynthesis pathway.

For example, in fluconazole-susceptible C. *albicans* fluconazole only partially inhibits ergosterol and completely blocks obtusifoliol synthesis, while voriconazole completely inhibits both ergosterol and obtusifoliol synthesis.[7]

Itraconazole and fluconazole may also reduce 3-ketoreductase, which catalyzes the reduction of the 3-ketosteroid obtusifolione to obtusifoliol in *C. neoformans*.[8] All azoles act much more slowly than polyenes. Thus they are used less often than polyenes in treatment of fulminating fungal infections. Some of the important azoles together with their indications, brand name and available formulation are listed in the Table 2.[1]

Table 2 Pharmacology of Azoles with example

Agents	Indications	Brand Name	Available Formulation
Itraconazole	I.V., oral capsule: Pulmonary and extra pulmonary blastomycosis; histoplasmosis, including chronic cavitary pulmonary disease and disseminated, nonmeningeal histoplasmosis; aspergillosis in patients who are refractory to or intolerant of amphotericin B therapy. Oral capsules only: Non-immunocompromised patients: treatment of onychomycosis of the toenail, with or without fingernail involvement, or of the fingernail alone, due to dermatophytes (tinea unguium). I.V., oral solution only: Empiric therapy of febrile neutropenic patients with suspected fungal infections. Oral solution only: Oropharyngeal and esophageal candidiasis.	Sporanox, (Janssen/ Ortho-McNeil)	IV, oral capsule, oral solution
Ketoconazole	Candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromoblastomycosis, and paracoccidioidomycosis; severe recalcitrant cutaneous dermatophytes infections that have not responded to topical therapy or oral griseofulvin, or in patients unable to take griseofulvin.	Nizoral (Janssen/ Ortho-McNeil; various)	Oral tablet
Voriconazole	Invasive aspergillosis; candidemia in nonneutropenic patients and the following Candida infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds; esophageal candidiasis; serious fungal infections caused by Scedosporium apiospermum (asexual form of Pseudallescheria boydii) and Fusarium spp, including F. solani, in patients intolerant of, or refractory to, other therapy.	Vfend, (Pfizer)	IV, oral tablet

Spectrum of Activity

Azoles have large spectrum of activity against yeasts and moulds. Though, as this therapeutic class expands, difference in spectrum of activity among the individual agents emerges. The disparity in spectrum of activity exhibited among different azoles may be attributed to variation in the inhibition of 14α-demethylase and secondary targets among species. Table 3 shows spectrum of activity of various azoles.

Table 3 Spectrum of activity of various azoles

Agent	Spectrum of activity
Fluconazole	a. *In-vitro* activity of fluconazole is generally considered fungistatic b. Relatively narrow spectrum of activity is limited to yeasts c. Very active against *Candida* species including *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. lusitaniae and m*uch less active against other *Candida* spp. d. *C. krusei* is inherently resistant, and species such as *C. glabrata* and C. *guilliermondii* have reduced susceptibilities to fluconazole e. Fluconazole also has activity against *C. neoformans* and *Coccidioides immitis* f. Fluconazole has no activity against Aspergillus *spp*., *Fusarium spp*. and the agents of zygomycosis.
Itraconazole	a. Fungicidal activity against filamentous fungi and some strains of *C. Neoformans* and is generally fungistatic against many yeasts b. Moderately to very active against most medically important fluconazole-susceptible and - resistant *Candida* species (except *C. Glabrata)* c. Modest activity against *C. Neoformans* d. Excellent in vitro activity against common dimorphic or endemic fungi including *C. Immitis*, *H. capsulatum*, *B. Dermatitidis*, and *S. Schenckii*. e. Good activity against many *Aspergillus* spp. But it has variable activity against *Fusarium* spp. and very limited activity against the agents of zygomycosis
Voriconazole	a. Fungicidal activity against most yeast and certain opportunistic fungi, and fungicidal activity against some non-albicans Candida spp. And C. neoformans. b. Very broad spectrum of activity against dermatophytes, yeasts, and moulds. c. Active against all Candida spp., including fluconazole-resistant C. Albicans, C. Glabrata, and C. Krusei d. More active than fluconazole against medically important Candida spp. (except C. Tropicalis) e. Very active against other yeasts, including C. Neoformans and most Trichosporon spp., including T. Asahii, but it is not very active against T. Beigelii/T. Cutaneum f. Excellent in vitro activity against Aspergillus spp. and is highly active against A. Fumigatus, A. Flavus, and A. Terreus. g. Active against many amphotericin-resistant moulds, including certain strains of Scedosporium apiospermum

Posaconazole	a. Similar to fluconazole, voriconazole has poor or no activity against the agents of zygomycosis. b. Fungicidal activity against non-albicans Candida species including C. Krusei, C. Inconspicua and C. Lusitaniae, but is fungistatic against C. Albicans, C. Glabrata, C. Tropicalis, C. Guilliermondii and C. Parapsilosis. c. Like voriconazole, posaconazole demonstrates in vitro fungicidal activity against Aspergillus spp. and C. Neoformans. d. More active than itraconazole and fluconazole against all Candida spp. And C. Neoformans. e. In vitro, posaconazole is the most active azole against Aspergillus spp. And is highly active against A. Fumigatus, A. flavus, and A. Terreus. f. Very potent activity against the dimorphic fungi including C. Immitis, H. Capsulatum, B. Dermatitidis and S. Schenckii. g. Variable activity against many amphotericin-resistant molds, including certain strains of Scedosporium apiospermum and P. Boydii, but is not active against Fusarium spp. h. Variable activity against the agents of zygomycosis.

Pharmacokinetics of Azoles

Chemically, azoles are lipophilic weak bases. All azoles have good relative or absolute bioavailability after oral administration (except the capsule form of itraconazole). Dissolution of ketoconazole and itraconazole in the stomach, administered as solid oral dosage forms are significantly affected by elevations in gastric pH.[9, 10] Azoles (except posaconazole) require extensive oxidative (CYP) metabolism to be eliminated from the body. Different the other triazoles, posaconazole undergoes minimal (2%) CYP metabolism; most of its metabolites are glucuronide conjugates formed by uridine diphosphate glucuronosyltransferase (UGT) pathways, mainly UGT1A4. [11, 12] Fluconazole is less lipophilic, and therefore it requires less oxidative (CYP) metabolism. The azoles are inhibitors of CYP3A4, the primary oxidative drug-metabolizing enzyme in humans. [13, 14] Though, the azoles all differ in their affinity for this enzyme. Fluconazole and voriconazole also inhibit CYP2C9/19 and fluconazole inhibits a UGT pathway (UGT2B7). [13-15] The significance of the interaction is unknown. Drug disposition is facilitated by a variety of transport proteins which are expressed in tissues throughout the body in humans. Azoles and echinocandins vary in their interactions with transport proteins.[16] Itraconazole, ketoconazole, and posaconazole interact with P-glycoprotein, the best-known efflux transport protein. Ketoconazole and itraconazole interact with another transporter, known as breast cancer resistance protein (BCRP). [16] The significance of these interactions with BCRP have not been fully elucidated, but they may, in part, explain certain interactions that before could not be sufficiently explained by interactions with CYP.

The azoles require extensive oxidative (CYP) metabolism to be excreted from the body. Only 2–4% of a dose administered PO appears unaffected in the urine. Itraconazole is metabolized to an active metabolite that may contribute significantly to antimicrobial activity. The biliary route is the major excretory pathway (>80%); 20% of the metabolites are eliminated in the urine. Drug disposition is facilitated by a variety of transport proteins which are expressed in tissues throughout the body in humans. The azoles vary in their interactions with transport proteins. The azoles appear to be extensively distributed in the body with detectable concentrations in saliva, milk and cerumen. Cerebrospinal fluid penetration is poor except for fluconazole, which reaches 50–90% of plasma concentrations. The rate of elimination of the azoles appears to be dose dependent: the greater the dose, the longer the elimination half- life. There is also biphasic elimination pattern with rapid elimination in the first 1–2 hr, then, a slower decline over the next 6–9 hr. Because of the long half-life and mechanism of action (impaired synthesis of the fungal cell membrane), time to efficacy may take longer than drugs that have more rapid actions as amphotericin B.

Toxicity of Azoles

The primary toxicities associated with the azoles involve the liver have been shown in the Table 4 and adverse effects in Table 5. These toxicities range from the common transient elevations in serum transaminases to the less common fulminant hepatoxicity and liver failure. Liver failure is rare but it may occur with any azole. [17-20]

Table 4 Toxicity of Azoles

Agent	Toxic effect
Voriconazole	a. Produces clinically significant transaminases abnormalities in approximately 13% of patients. b. Produces visual disturbances in approximately 20% to 30% of subjects in clinical trials.
Itraconazole	a. Has been associated with the development of congestive heart failure. In such case risk and benefits of using itraconazole for non–life-threatening infection must be seriously considered.
Ketoconazole	a. Produce endocrine abnormalities that lead to gynecomastia and adrenocortical insufficiency (because of its lack of selectivity for fungal CYP).

Adverse Effects of Azole

The azoles give PO result in many adverse effects. The adverse effects include cardiopulmonary (hypotension, peripheral/ pulmonary edema), CNS (dizziness, headache, seizure), dermatologic/hypersensitivity (anaphylaxis, eosinophilia, pruritus, rash), electrolyte disturbances (hypokalemia), gastrointestinal (abdominal pain/dyspepsia, diarrhea, disguise, nausea/vomiting), hematological (anemia, myelosuppression, thrombocytopenia), Hepatic (hepatic necrosis/hepatitis/cholestasis) and miscellaneous (alopecia, fever). But nausea, vomiting, and hepatic dysfunction can develop; particularly with ketoconazole.[21] Altered testosterone and cortisol metabolism have been reported, particularly with ketoconazole.[21] Reproductive disorders related to ketoconazole administration may be seen in dogs. Voriconazole is associated with a number of adverse effects in humans including vision disturbances.

Table 5 Adverse Effects of Azoles

Agent	Adverse Effects
Fluconazole	a. Cardiopulmonary: Hypotension (rare), peripheral/pulmonary edema (rare) b. CNS: Dizziness (rare), headache, seizure (rare) c. Dermatologic/Hypersensitivity: Anaphylaxis, eosinophilia, pruritus, rash d. Electrolyte Disturbances: Hypokalemia (rare) e. Gastrointestinal: Abdominal pain/dyspepsia, diarrhea, dysgeusia, nausea/vomiting f. Hematologic: Anemia (rare), myelosuppression (rare), thrombocytopenia (rare) g. Hepatic: LFT; hepatic

	necrosis/hepatitis/cholestasis h. Miscellaneous**:** Alopecia, fever (rare).
Itraconazole	a. Cardiopulmonary**:** Congestive heart failure, hypertension (rare), peripheral/pulmonary edema, tachycardia (rare), tachypnea (rare) b. CNS**:** Dizziness (rare), headache c. Dermatologic/Hypersensitivity: Anaphylaxis, eosinophilia, pruritus, rash d. Electrolyte Disturbances: Hypokalemia (rare) e. Endocrine: Altered hormone levels (rare), gynecomastia (rare) f. Gastrointestinal: Abdominal pain/dyspepsia, diarrhea, flatulence (rare), nausea/vomiting g. Hepatic: LFT, hepatic necrosis/hepatitis/cholestasis h. Miscellaneous: Fever (rare), alopecia (rare)
Ketoconazole	a. Cardiopulmonary: Hypertension (rare) b. CNS**:** Headache c. Dermatologic/Hypersensitivity**:** Anaphylaxis, eosinophilia, pruritus, rash d. Endocrine**:** Adrenocortical insufficiency, altered hormone levels, gynecomastia, inhibition of cortisol synthesis e. Gastrointestinal**:** Abdominal pain/dyspepsia, diarrhea, flatulence (rare), nausea/vomiting; f. Hematologic**:** Anemia (rare), myelosuppression (rare), thrombocytopenia g. Hepatic**:** LFT, hepatic necrosis/hepatitis/cholestasis h. Miscellaneous**:** Fever (rare).
Voriconazole	a. Acute Infusion Reactions: Fever (rare), nausea/vomiting (rare), visual disturbances b. Cardiopulmonary: Congestive heart failure (rare), hypertension (rare), hypotension (rare), peripheral/pulmonary edema (rare), tachycardia (rare) c. CNS**:** Dizziness (rare), hallucinations (rare), headache, seizure (rare) d. Dermatologic/Hypersensitivity**:** Anaphylaxis eosinophilia.

Drug-Drug Interactions of Azoles

Drug interactions associated with the azoles result from several diverse mechanisms. These agents can act together with drugs through different mechanisms (e.g. pharmacodynamics, pH, complexation and electrostatic interactions, CYP and P-glycoprotein). Interactions involving the azoles are pharmacokinetic and result as a consequence of their physicochemical properties. [22, 23] Ketoconazole and itraconazole are subject to pH-based and metabolic interactions. Drugs that will likely interact with these azoles include agents that are cationic or increase gastric pH or are lipophilic CYP3A4 substrates with poor oral availability. All azoles are weak bases and at elevated pH values, weakly basic compounds dissolve more slowly.

So, the absorption of azoles such as the capsule form of itraconazole is influenced by alterations in gastric pH. Many of the azoles are lipophilic and thus they are subjected to interactions involving their biotransformation and disposition. Fluconazole is hydrophilic and is highly soluble in water and therefore, compared to the other azoles, it requires much less biotransformation to be eliminated from the body. Itraconazole, voriconazole and posaconazole are highly lipophilic and have limited aqueous solubility. Therefore, these azoles must undergo extensive enzymatic conversion to more polar metabolites in order to be eliminated from the body.

The azoles may be used alongside with amphotericin B or 5-flucytosine to potentiate its antifungal activity. The azoles are substrates for p-glycoprotein transport protein and may compete with other substrates, causing higher concentrations Azoles in general and ketoconazole in particular, inhibit the metabolism of some drugs and if administered concurrently, their concentrations may be higher than anticipated.

Resistance of Azoles

In the 1990s, many human immunodeficiency virus (HIV)-infected patients received long-term, low-level azole antifungal therapy, which resulted in azole-resistant isolates of *C. albicans.*[24] One study documented azole resistance in up to one-third of the oral *C. albicans* isolates from HIV-positive patients. Since the advances in growth of the azole group of antifungal compound for the treatment of fungal infections, it has got extensive use. So, with wide use resistance to these agents has been reported, particularly fluconazole. [24, 25] Resistance to the azoles is attributed to quantitative or qualitative modifications of target enzymes, reduced access of the drug to the target enzyme or by a combination of these mechanisms.

Qualitative modifications in target enzymes result from point mutations in ERG11, the gene responsible for producing 14α-demethylase, which is the principal target of the azoles. On the other hand, the different chemical structures of the azoles may also contribute to this differential activity. Quantitative modifications in target enzymes also result from mutations in ERG11. Over expression of the gene results in over-production of the target enzymes, this then necessitates higher intracellular azole concentrations to inhibit the entire target enzyme.

In the last few years, several molecular mechanisms by which *C. albicans* develops resistance to antifungal drugs has been elucidated . The azoles including fluconazole target lanosterol 14α- demethylase, the product of the *ERG11* gene. Erg11p is one of the enzymes in the biosynthesis of ergosterol, the major sterol of fungal membranes and an analogue of cholesterol in mammalian systems. Antifungal drug resistance has been associated with point mutations and increased levels of expression of the *ERG11* gene.[26] Evidence is accumulating that changes in other enzymes in the ergosterol biosynthetic pathway can also contribute to resistance. Drug efflux from the cells is another component of resistance in *C. albicans*, as over expression of two types of efflux pump has been correlated with antifungal resistance. The ABC transporter genes *CDR1* and *CDR2* encode ATP-dependent efflux pumps that are over expressed in many azole-resistant isolates. Deletion of these genes results in hypersensitivity to azoles. The major facilitator gene *MDR1* encodes a pump that uses the proton motive force at the membrane to transport drugs and other compounds across the plasma membrane. Over expression of this pump is also associated with resistance and deletion results in hypersensitivity to the azoles. Moreover, another major facilitator gene, *FLU1*, was identified in *C. albicans*. This gene increases the level of azole resistance when it is expressed in *Saccharomyces cerevisiae* and increases the level of susceptibility when it is deleted from *C. albicans*, but over

expression of the gene has not yet been correlated with azole resistance in clinical isolates of *C. albicans.* [24-26] The changes in the level of susceptibility are associated with each of these molecular alterations.

The level of susceptibility for fungal cells is usually measured as the MIC, and the MIC determination method has recently been standardized for reproducibility and inter laboratory consistency. In recent years, resistance to antifungal drugs has been documented in other patient populations such as bone marrow transplant recipients. In a clinical setting, there are many reasons why a fungal infection does not respond to antifungal drugs, including the immune status of the patient, the characteristics of the drug, and the susceptibility of the fungus to the drug.[26] The known molecular mechanisms of resistance are best illustrated by a series of 17 isolates from an HIV-infected patient. Resistance developed over time in this series of isolates.

Up to date, mechanisms of resistance have been determined in clinical isolates in which matched sets of resistant and susceptible isolates of the same strain were analyzed. In the most recently published work, the molecular mechanisms of resistance in matched sets of susceptible and resistant isolates of the same strain from an HIV-infected patient population were investigated.[27] The study found that 85% of isolates over expressed efflux pumps, 65% of isolates had mutations in *ERG11* and 35% of isolates over expressed *ERG11*. Most of the point mutations identified in that study were previously described in a survey of point mutations in *ERG11*.

In summary, diverse mechanisms add to the resistance of antifungal agents. These mechanisms include modification of ERG11 gene at the molecular level (gene mutation, conversion and over expression), over expression of specific drug efflux pumps, alteration in sterol biosynthesis, and reduction in the intracellular concentration of target enzymes.

CONCLUSION

The occurrence of infection with invasive mycoses continues to increase with the increasing immunosuppressed patients. The therapy of fungal infections has undergone an explosive period of development in recent years. The azole group of compounds has provided excellent therapy in the treatment of most clinically important mycoses. Clinicians must recognize the differences in toxicity and potential for drug–drug interactions to use these agents optimally. Additional advances in antifungal chemotherapy will be necessary to improve management of invasive mycoses in the future.

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