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REVIEW ARTICLE

Antifungal Pharmacotherapy and Hepatic Safety: Mechanisms of Drug-Induced Liver Injury (DILI) and Risk Mitigation

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Abstract

The growing prevalence of invasive fungal infections (IFIs), especially among immunocompromised patients, has resulted in increased reliance on systemic antifungal therapies. Hepatotoxicity is still a serious clinical problem even with improvements in treatment results. This study consolidates the mechanisms, incidence rates and risk factors associated with drug-induced liver injury (DILI) across various antifungal classes, including flucytosine, azoles, polyenes, echinocandins and allylamines. Triazole antifungals, such as voriconazole, fluconazole and ketoconazole are particularly implicated because of their substantial hepatic metabolism via cytochrome P450 enzymes and potential for interactions between drugs. Direct hepatocyte damage, immune-mediated responses, mitochondrial malfunction and changes in cytokine signalling are some of the mechanisms of hepatotoxicity. Terbinafine and other echinocandins and allylamines can also be hepatotoxic, particularly when combined with polypharmacy and pre-existing liver illness. Acute liver failure and asymptomatic liver enzyme increases are examples of clinical symptoms. To maximise treatment while reducing hepatic side effects, a thorough understanding of antifungal pharmacokinetics, metabolism and patient-related risk factors is necessary.

Key words: Antifungal agents; Drug-induced liver injury; Hepatotoxicity; Polypharmacy; Triazoles.

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Introduction

Infections with fungi have become very common and severe in humans in recent years, impacting people of all ages. The eukaryotic character of fungi, which resemble mammalian cells, makes it difficult to design effective antifungal treatments. Advancements in azole antifungals, including the development of safer agents and enhanced formulations, have significantly improved the management of both superficial and systemic fungal infections. Topical formulations are still frequently used for surface infections, but systemic antifungal medications are now commonly employed, either orally or intravenously. Triazoles like voriconazole, fluconazole and ketoconazole are among the systemic antifungals that offer more therapy options, but they also have a high potential for hepatotoxicity. One of the biggest concerns with antifungal pharmacotherapy is drug-induced liver damage (DILI). DILI refers to elevations in serum liver enzymes, specifically alanine aminotransferase (ALT) or aspartate aminotransferase (AST) exceeding three times

the upper limit of normal (ULN), alkaline phosphatase (ALP) levels more than twice the ULN, or total bilirubin concentrations surpassing twice the ULN. It is advised to stop using the offending substance within 48 to 72 hours if liver enzyme levels steadily rise, especially if there are no other known causes.

Hepatotoxicity can manifest as cholestatic injury (higher ALP), hepatocellular injury (higher ALT), or a combination of these. DILI is caused by several processes, including immune-mediated responses, apoptosis, poor bile transport, cytochrome P450 enzyme suppression, disruption of calcium homeostasis that causes hepatocyte lysis and mitochondrial dysfunction that causes oxidative stress and lipid buildup.

Even so, fungal infections in humans and animals have increased in frequency and severity in recent years. Since fungi are eukaryotic organisms, the development of new drugs to combat them has been limited by their resemblance to mammalian cells. All ages are susceptible to these infections.[1] These medications are now available in new formulations. Immunosuppressive drugs nowadays, a variety of antifungal agents are applied topically or administered systemically. Systemic, mucosal and cutaneous fungal infections are treated with oral or intravenous systemic medications. Skin and mucosal fungal diseases (not systemic infections) can also be treated with topical antifungal medications.

Hepatotoxicity, or liver injury, is defined as an elevation in either serum ALT or AST levels exceeding three times the ULN, ALP levels more than twice the ULN, or total bilirubin levels greater than twice the ULN.[2, 3] If ALT or AST values continue to rise or if total bilirubin levels stay at least twice the ULN, the drug should be stopped within 48 to 72 hours, as long as no other possible causes of liver damage have been identified. Though these criteria involve subjects with conventional ALT values (≤ 150 % ULN) at standard, the increase of ALT 2-fold in patients with pre-existing liver provocative test. It has been point by point that a fivefold stature of ALT as signal of conceivably DILI and this is the degree to end the medication.[4] Other than having non-alcoholic fatty liver ailment, hepatitis C, loads of press (frequently caused by different blood transfusions), cholestasis (not uncommon among include up to parenteral nutrition patients) and alcohol abuse have been found to be related to DILI.[5] It is in addition worth saying that DILI is the most frequent cause for toxicities driving to withdrawal of a steady exhibit and this is to an awesome degree influenced by the truth that, routinely, clinical enrolment trials have included less than 3000 subjects. In this setting, DILI with a rate more critical than 1:3,000 can as were revealed in the post-marketing surveillance.

DILI can be hepatocellular (basically early ALT stature; ALT-to-ALP extent ≥ 5) or cholestatic (early increase in Tall Mountain; ALT-to-ALP ≤ 2). Regardless, these two types of harm are not mutually exclusive and combination types are seen as frequently as possible. In addition to the so-called DILI and DILI associated with peaceful nature, there are just six distinct ways that unconventional DILI might occur: (i) the disruption of cellular calcium homeostasis, which results in hepatocyte lysis; (ii) the disruption of transport pumps, which count multidrug-resistance-associated protein (MRP3) and cause cholestasis and alter actin fibres close to the canaliculus; (iii) the disintegration of chemical structures, including cytochrome P450 (CYP450), following their interaction with medication; and (iv) the activation of immune components once the enzyme-drug addicts are arranged and relocated to the hepatocyte surface, (v) apoptotic progression as a result of immune-mediated damage activation and (vi) interaction with mitochondrial function helps the hepatic cell manage oxidative stress, lactic acidosis and triglyceride accumulation. Since clinical studies currently determine the measurements of each sedate, dose-dependent DILI is also a problem for voriconazole, as was later investigated.[6]

Reactions catalysed by the aminotransferases

ALT and AST catalyse the transfer of an amino group from amino acids to α-ketoglutarate, producing L-glutamate and either pyruvate (via ALT) or oxaloacetate (via AST). This transamination reaction involves the exchange of a keto group and an amino group and requires pyridoxal 5'-phosphate (PLP), a vitamin B6 derivative, as a coenzyme. Notably, these reactions are reversible and play critical roles beyond amino acid metabolism, contributing to various cellular

functions, including the maintenance of energy homeostasis.

One of the most critical physiological roles of ALT lies in the alanine-glucose cycle. In skeletal muscle, ALT facilitates the transamination of pyruvate to form alanine, utilising an amino group from glutamate. Alanine is then transported via the bloodstream to the liver, where hepatocyte-derived ALT reconverts it into pyruvate, which subsequently enters gluconeogenesis to produce glucose. This cycle plays a vital role in maintaining blood glucose levels during metabolic stress, such as fasting or intense physical activity. Additionally, emerging evidence suggests that the mitochondrial isoform of ALT may be particularly important for hepatic gluconeogenesis under specific conditions. In contrast, the primary physiological function of AST is the regulation of the intracellular NAD^+/NADH ratio. AST is a key component of the malate-aspartate shuttle, which facilitates the transfer of reducing equivalents by oxidising cytosolic NADH and reducing mitochondrial NAD^+, thereby supporting sustained glycolytic activity.[7] The galactose tolerance test serves as a diagnostic tool to evaluate hepatic capacity for converting galactose into glycogen. Additionally, when serum samples are mixed with specific reagents-such as cephalin-cholesterol complexes extracted from sheep brain—flocculation may occur, providing insight into alterations in serum protein composition associated with liver disease.[8]

Transaminase measurements were rapidly adopted by clinical laboratories due to their diagnostic utility. Although subsequent studies consistently demonstrated elevated AST levels in patients with liver disease, ALT emerged as a more reliable marker of hepatic injury, owing to its significantly higher activity in the liver compared to muscle tissue. ALT's liver specificity, coupled with the simplicity of its assay, contributed to its widespread clinical use. Since the initial identification of AST and ALT, the repertoire of liver injury biomarkers has remained relatively static, with the notable exception of gamma-glutamyl transpeptidase (GGT), introduced in the 1960s as an additional indicator of hepatic dysfunction. This stagnation contrasts sharply with the evolving landscape of biomarkers for other organ systems, such as the heart and kidneys, where markers for conditions like acute myocardial infarction have undergone continuous refinement.[9]

Emerging biomarker technologies

Over the past decade, there has been a significant surge in interest surrounding the development of novel biomarkers for liver injury. This growing attention is driven by three key needs: the demand for sensitive, non-invasive biomarkers capable of detecting idiosyncratic hepatotoxicity during early drug trials; the necessity for predictive biomarkers that can inform clinical outcomes in patients with established liver injury; and the desire for translational biomarkers that can bridge mechanistic insights from rodent models to human physiology. Among available models, acetaminophen (APAP) overdose has emerged as the most widely used for biomarker discovery across all three domains. Although APAP-induced injury is not representative of idiosyncratic toxicity and may have limited relevance for early drug screening, the model remains clinically pertinent and experimentally convenient. In mice, a single high dose of APAP induces rapid hepatotoxicity and human clinical specimens from APAP overdose are more accessible than those from other DILI. APAP overdose is also a leading cause of acute liver failure (ALF) and ALF-related mortality, making it a valuable source for biomarker research. Despite its widespread use, few studies have rigorously evaluated the positive and negative predictive values of emerging biomarkers. However, many investigations comparing ALT and AST with newer markers have demonstrated superior performance of the latter in detecting liver injury and predicting outcomes. The aim of this review was not to diminish the importance of aminotransferases, which will remain essential tools in liver diagnostics, but to deepen understanding of their limitations and explore complementary or alternative biomarkers. Several novel indicators—such as glutamate dehydrogenase (GLDH), mitochondrial DNA (mtDNA), nuclear DNA fragments, keratin-18 (K18) and high-mobility group box 1 (HMGB1)—have shown promise in revealing specific pathophysiological mechanisms, enhancing their value in translational studies. Nonetheless, improved predictive accuracy is needed before these biomarkers can be adopted into routine clinical practice. Enhancing negative predictive value (NPV) for patient triage and positive predictive value (PPV) for forecasting poor outcomes may be achieved through multi-biomarker panels or the discovery of entirely new markers. Further research is also required to determine whether

any of these emerging biomarkers can reliably predict idiosyncratic toxicity in drug development settings.[10]

Polyenes

A broad-spectrum antifungal medication called amphotericin B deoxycholate (DAMB) is used to treat infections that are potentially fatal and brought on by *Aspergillus*, *Candida*, *Cryptococcus* and other fungus. Significant hepatotoxicity is not a frequent side effect of DAMB, despite its wide clinical use. The medication is eliminated unaltered in urine and bile and mostly builds up in the organs of the reticuloendothelial system.

When it does occur, its interaction with cholesterol in mammalian cell membranes may cause hepatotoxicity.

Amphotericin B deoxycholate (DAMB) is a widely used broad-spectrum fungicidal agent for the treatment of life-threatening invasive fungal diseases (IFDs), including those caused by *Candida, Aspergillus, Cryptococcus, Histoplasma, Blastomyces, Coccidioides* and other pathogenic fungi. It remains a critical therapeutic option, particularly in resource-limited settings and less-developed countries (LDCs), where alternative antifungal treatments may be inaccessible or unaffordable. The utility of DAMB is impaired by tall nephrotoxicity and infusion-related reactions. Undoubtedly in show disdain toward of the truth that it has been utilised for more than 50 a long time in the clinic, hepatic brokenness is not one of the well-known typical and clinically imperative side impacts of this polyene macrolide.[11] Following the organisation of DAMB, amphotericin B is released from the carrier and collects fundamentally in MPS organs, whereas it is unaltered in pee and bile.[12] DILI of amphotericin B may result in the substance's interfacing to cholesterol of mammalian-cell layers, acknowledged to talk to the preeminent nuclear instrument essential human hurtfulness of amphotericin B.

Azoles

Azole antifungals—including imidazoles (such as clotrimazole, miconazole and ketoconazole) and triazoles (like fluconazole, itraconazole, voriconazole and posaconazole)—inhibit fungal 14α-sterol demethylase, thereby interfering with ergosterol biosynthesis. However, they cause serious hepatotoxicity and medication interactions when they interact with human cytochrome P450 enzymes, The superfamily of membrane-bound haemoprotein isozymes known as cytochrome P450 is divided into several categories. Despite being present in most body tissues, the liver, kidneys and intestines contain the highest concentration of CYP enzymes. Ninety percent of drug metabolism is accounted for by six of the 57 isozymes that have been discovered thus far. The six key cytochrome P450 isozymes—CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4—play a vital role in drug metabolism. Identifying which of these isozymes are affected during drug development is essential, as different drugs interact with different enzymes, influencing efficacy, safety and potential drug–drug interactions. Depending on the enzyme and substrate, CYP enzymes can conduct a wide range of reactions, each with slightly distinct variants. The main function of CYP as monooxygenases is to add an oxygen atom to the substrate. In general, a few easy steps determine the mechanism that CYP uses to catalyse processes. A heme-iron centre makes up the active site of CYP enzymes. A cysteine thiolate molecule binds the iron component to the protein. The enzyme's active site undergoes a conformational change when the substrate or substrates attach to the heme group. The transfer of electrons from NAD(P)H is then carried out by reductases. After iron is reduced, oxygen attaches itself to the ferrous-heme group. The Fe-O_2 group, also referred to as a peroxide state, is created by adding another electron through reduction. The peroxide group is short-lived because it undergoes two protonation's, releasing water and P450 Compound 1 (FeO^{3+}). The required molecules can be obtained through this activity and further hydroxylated to a more hydrophilic, excretable form. The mechanism's outcome looks like this:

$$NAD(P)+ + H_2O + ROH \rightarrow O_2 + NAD(P)H + H+ + RH$$

Drugs and other substances with a free polar group can bypass step I and move straight on to phase-II for conjugation.[13, 14]

Cytochrome P450 (CYP) enzymes are crucial for drug metabolism and are affected by inhibitors, inducers and substrates. CYP1A2 is inhibited by ciprofloxacin, induced by tobacco and metabolises caffeine. CYP2C9 is inhibited by fluconazole, induced by rifampicin and metabolises ibuprofen. CYP2C19 is inhibited by isoniazid, induced by

phenytoin and metabolises omeprazole. CYP2D6 is inhibited by fluoxetine, has no known inducers and metabolises codeine. CYP2E1 is induced by ethanol, with acetaminophen as a substrate and no strong inhibitors. CYP3A4, the most important isoform, is inhibited by ketoconazole, induced by carbamazepine and metabolises statins.[15]

It is important to note that numerous drugs function simultaneously as inducers, inhibitors and substrates of specific isozymes. To avoid redundancy, such agents have not been listed multiple times in this context especially CYP3A4.[16] While voriconazole and posaconazole have broader efficacy, including against azole-resistant strains, fluconazole and itraconazole are effective against *Aspergillus* and *Candida species*. Despite its effectiveness, ketoconazole inhibits the processes involved in drug metabolism and steroid production, which can lead to hepatotoxicity and endocrine disorders. Triazoles have been linked to acute liver failure and cholestatic and hepatocellular damage, particularly in those who are susceptible or use them for an extended period. High plasma drug concentrations, polypharmacy, pre-existing liver disease and genetic factors all raise the risk.

The purpose of this review is to provide an explanation of the extent of liver injury by azoles, description of the difference in damage among them and a proposal for holistic clinical judgment for liver injury using azoles. For almost twenty years, azoles have been administered for different fungal infections. There are two types of azoles, they are triazoles and imidazole's. Imidazole's include clotrimazole, miconazole and ketoconazole. Triazoles include itraconazole, posaconazole, voriconazole, azaconazole, terconazole and likely fluconazole. Azoles are 14 alpha-sterol demethylases inhibitors, which may have significant interactions between drugs, since the P450 CYP/ inhibition is intensive with azoles. Other action mechanisms of these drugs exist; however, including the following: these drugs are believed to be able to block fungal cell death results from cellular respiration through membrane adhesion, changes in membrane permeability and toxicity interactions with phospholipids in the fungal cell membrane.[17] Topical imidazole's come in a variety of forms, including shampoos, lotions, lozenges, vaginal pills, solutions and creams. The first oral azole medication on the market for treating fungal infections, ketoconazole, exhibits its broad-spectrum action against a variety of *Candida* infections. When considering all azoles, fluconazole, a triazole, the original triazole antifungal, has several distinct advantages and additional properties compared to the other azoles. One of the other advantages is an increased antifungal spectrum. Fluconazole is efficacious for multiple *Candida* and *Cryptococcus* infections.[18] Oral and intravenous itraconazole are the same as fluconazole. Its spectrum of action is as in fluconazole but is also active against *Aspergillus spp.* Voriconazole is also approved by the FDA in 2002. This agent also has a broad spectrum of antifungal activity and shows strong antifungal efficacy against *Aspergillus*, particularly amphotericin B-resistant *Aspergillus*.[19] Ph may not have to be acidic to maximising the absorption of voriconazole. Moreover, it is more bioavailable than ketoconazole and itraconazole. Voriconazole should be taken 1 h before, during, or up to 1 to 2 h following a meal as fat-containing foods decrease their absorption. A proportion of the patients treated with voriconazole suffer transients' visual disturbances, like photophobia, reduced vision and/or altered colour vision. These adverse responses are not associated with the form of administration of the drug (oral or intravenous).[20]

As the most recent of the triazole antifungal agents, posaconazole was approved in 2006 and has a wide antifungal spectrum, including against the known azole-resistant *Candida spp*. Posaconazole in contrast to voriconazole, has *in vitro* activity against zygomycetes. Posaconazole formulations include an oral suspension, tablets and an intravenous dosage form, with the oral solution having low oral bioavailability. If this medicine is orally administrated as a fatty food-containing dosage form, its bioavailability will be enhanced up to 400 %.[21] The antifungal effect of the azoles is caused by a decreased synthesis of ergosterol in the fungal membrane. The specificity of azoles is determined by the greater vulnerability of these drugs than human cytochrome P450 enzymes are to fungal infection. Yet like any drugs, azoles may produce adverse effects in some patients.

At 228.0 (95 % CI 33.9, 933.0), ketoconazole had the highest relative risk of any antifungal when compared to the risk among nonusers. The relative risks for terbinafine and itraconazole were 4.2 (0.2, 24.9) and 17.7 (2.6, 72.6), respectively. The first oral azole to be used in clinical settings was ketoconazole. Compared to more contemporary medications, it is less successful at blocking mammalian cytochrome P450 enzymes. In other

words, it is less selective for the fungal P450 than the novel azoles.[22] There are two implications to this. The first is that ketoconazole inhibits cytochrome P450 enzymes, which in turn inhibits the manufacture of steroid hormones. This results in significant endocrine abnormalities, including infertility and menstrual disorders. Second, other medicines undergo toxic alterations in metabolism. Most ketoconazole side effects are dose related. Its adverse effects include gynecomastia, headache, dizziness, pruritus, nausea, vomiting, stomach discomfort, diarrhoea, constipation, bloating.[23]

Hepatotoxicity induced by a drug in the human or DILI is a major liver disease concern and proper assessment of the reaction is one of the most important issues with respect to the critical assessment. DILI is rare, but OTC drugs, herbal products, or supplements are some of the antecedents.[24] The side effects from DILI are predictable or unpredictable, and, unfortunately, unpredictable is usually how they are. Drugs, eg paracetamol have potential of inducing liver injury that has predictable kinetics and completes within a short period, commonly a few days.[25] The interval between drug exposure and unpredictable hepatic injury is an average of 1 week to 2 months (eg phenytoin), or it can be a long interval of 1 year (eg isoniazid).[26] These effects happen in between 1/1,000 - 1/10,000 sufferers given usual dosages associated with various drugs. The chemical nature of the drug, other environmental factors (such as concomitant use of the drug with alcohol), age, gender, comorbidities not least diabetes and genetic factors, among others, contribute to DILI.[27] The incidence of DILI appears to be on the rise in the general population.[28] In relation to drug induced hepatotoxicity, it is important to note some considerations in patient assessment for these conditions such as: the pattern involved in liver injury, the time interval for the onset of symptoms, the presence or absence of hypersensitivity and toxic manifestations after discontinuation of the drug.[29] It is most likely to occur in people who have a genetic disposition toward the disease. These changes in drug metabolism and excretion can result in subsequent processes that occur within cells, including the production of oxidative stress, necrosis, apoptosis, protein haptenization and immune response triggering the mechanism of DILI appears to be dominated by direct hepatocytotoxicity and a few immune system reactions. Multiple chemical reactions can also target electrophilic compounds or free radical drug metabolites.[30] Protein dysfunction, lipid peroxidation, DNA damage and oxidative stress can all result from these reactive metabolites' ability to bind to proteins, lipids and nucleic acids. By having a direct impact on mitochondrial ATP synthesis, they may also result in a reduction in ATP production. Over time, the liver may fail, the cell may die and these functions will be disturbed. Through immunogenic and tolerant immune responses, innate immune cells—such as neutrophils, dendritic cells, natural killer T (NKT) cells, Kupffer cells and natural killer (NK) cells—are implicated in the preservation of liver homeostasis.

RLU-induced liver injury can trigger signalling cells, including NK, NKT cells and KC cells of the innate immune system. By producing pro-inflammatory mediators and secreting chemokines, the cells cause liver damage to develop.[30] Additionally, DILI triggers the release of inflammatory cytokines, such as tumour necrosis factor (TNF), interleukin 1 (IL-1) and interferon (IFN-), which have been implicated in tissue injury. Anti-inflammatory cytokines like IL-10, IL-6 and IL-13 are also protective and stop liver damage. The proportion of pro-inflammatory to anti-inflammatory cytokines is a key factor in determining how severe and sensitive liver damage.[31] By targeting certain cytokines, some illnesses, including influenza, hepatitis A and C and HIV, can also alter the severity of DILI.[32]

In addition, humoral immunity, particularly about antibody-mediated (Ab-mediated) responses, contributes to hepatotoxicity. Although it is still unclear how humoral immunity contributes to idiosyncratic DILI, some research has shown that the serum of participants has autoantibodies and antidrug antibodies (ADAs). Liver cells are markedly cytotoxic in DILI patients.[33] Fulminant hepatitis, acute and chronic hepatitis, ductopenia, cholestasis, steatosis (steatohepatitis, macrovascular, or microvascular steatosis) and granulomatous hepatitis are among the clinical and pathologic manifestations of hepatotoxicity.[34] Both dose-dependent and intrinsic DILI and non-dose-dependent or DILI have incorporated drug compounds as causative agents of liver impairment. For example, NSAIDs and amoxicillin-clavulanate, for flucloxacillin for DILI[35] and isoniazid, results in over 50 % cases of acute liver failure are of the result of DILI, with acetaminophen-induced hepatotoxicity being the commonest form of acetaminophen hepatotoxicity.

Rising mortality

In non-acetaminophen-induced hepatoxicity, patients being treated for acute secondary liver failure due to drugs are dying. The incidence of liver transplantation following DILI is around 10 %. The presence of jaundice in a patient with DILI who has elevated transaminases is associated with a 10 % greater mortality. Remember to keep in mind any drugs or chemicals that can cause hepatic failure. For this reason, the collection of an accurate drug history is key in the assessment of patients with hepatocellular or cholestatic liver disease.[36] Nevertheless, their toxicology mechanisms remain largely unknown. The hepatotoxicity of ketoconazole has been most extensively studied in laboratory animals and humans. Since these belong to the same class, mechanisms of hepatotoxicity by ketoconazole provide a framework to study mechanisms of azoles induced hepatotoxicity. As reported in various studies, people are exposed to triazole pesticides in multiple ways and this may result in injury, such as neural damage as well.[37] The suppression of CYP enzymes accounts for a large portion of fungicide toxicity in animals. Triazole changes the expression of several CYP genes in the liver, such as xenobiotic-metabolising enzyme (XME), CYP51, CYP2c, CYP3a and several isoforms. It prevents cytochrome 3P51 (CYP51) from doing its job. This cytochrome takes involved in the transformation of lanosterol into ergosterol in yeasts and fungi.

Triazole antifungals exert their therapeutic effect by inhibiting the fungal ergosterol biosynthesis pathway, specifically targeting the enzyme 14α-sterol demethylase (CYP51). This inhibition leads to a reduction in ergosterol, a vital sterol component of the fungal cell membrane, thereby compromising membrane integrity and causing cell death. However, in mammals, certain triazoles can also interfere with steroid hormone synthesis due to their impact on cytochrome P450 enzymes involved in endocrine regulation. Notably, some triazoles influence the expression of genes regulated by the constitutive androstane receptor (CAR), a nuclear receptor that governs energy balance, drug metabolism and cancer progression. By modulating CAR target gene transcription, these compounds may have broader physiological effects beyond their antifungal activity, potentially affecting hepatic enzyme function and metabolic homeostasis.[38] Based on these studies of liver tissue, triazoles have been found to activate nuclear receptors CAR and pregnane X receptor (PXR) in the liver, modulate CYPs and oxidative stress, disrupt cell signalling and cholesterol biosynthesis and induce cellular growth, proliferation, single cell necrosis, fat vacuolation and apoptosis. Studies have shown that triazole causes weight gain and hepatic enlargement. Its long-term toxicity also causes liver cancers. However, triazoles can harm tissues and cause medication interactions in the liver, kidneys and gastrointestinal tract. It was discovered that the human genome has fifty-seven CYP genes, fifteen of which are involved in drug metabolism. CYP3A4, 2C19 and 2C9 are among the several CYPs that alter triazole biodegradation. Between 30 and 60 percent of the hepatic CYP is accounted for by CYP3A4. By blocking hepatic CYP, triazole stops other medications from being bio transformed, which can result in interactions that are clinically relevant. Among the pharmacological classes with which triazoles interact, immunosuppressors, statins, anxiolytics, warfarin, antiretrovirals and benzodiazepines were the most significant clinical interactions of the other medications that prevent deformation. Some of these combinations cause liver function to be compromised and are highly toxic. The exact metabolism of triazoles and their impact on liver tissue are little understood and more research is expected in the future. Several factors, such as underlying liver disease, genetic susceptibility, concomitant administration of other hepatotoxic treatments, azole dose and plasma drug levels and infectious liver damage brought on by fungi, may affect the risk of hepatotoxicity caused by these medications.[39] Hepatotoxicity due to itraconazole, flucytosine and terbinafine is more frequent than amphotericin B. The antifungal agent that is most frequently associated with hepatotoxicity is ketoconazole. Hepatotoxicity due to antifungal agents usually resolve spontaneously upon cessation of the drug.

Azole antifungals have recently been linked to DILI; according to the international databases of pharmaceuticals and adverse events (2011–2014), 18 of these medications were responsible for 2.8 % of all DILI cases, including 4 cases of acute liver failure. Hepatotoxicity brought on by azoles can occur at any point after the start of azole therapy, although some reports indicate that this side effect typically manifests within the first month of treatment. Clinical and biochemical changes return to normal once these drugs are stopped. However, there have been

some reports of instances with fulminant hepatic failure, either with or without hepatic necrosis.[40] Even after considering structural similarities, only a few examples of cross-reactivity among the azoles have been reported.[41, 42]

Echinocandins

Echinocandins that inhibit 1,3-D-glucan production in fungal cell walls include caspofungin, micafungin and anidulafungin. They are safer in terms of hepatic metabolism since they interact with CYP450 enzymes less frequently. Nonetheless, mild to moderate increases of liver enzymes have been documented; the incidence of caspofungin is higher than that of other echinocandins.

Echinocandins are a distinctive class of injectable, semisynthetic amphiphilic lipopeptides that exert antifungal activity by noncompetitively inhibiting the enzyme β-(1,3)-D-glucan synthase, thereby disrupting the synthesis of 1,3-D-glucan—a critical component of the fungal cell wall. This mechanism compromises cell wall integrity, leading to osmotic instability and cell death, particularly in *Candida* and *Aspergillus* species. Due to their poor oral bioavailability, echinocandins are administered intravenously and are especially valuable in treating invasive candidiasis and aspergillosis. Over the past decade, three echinocandin agents—micafungin, caspofungin and anidulafungin—have been developed and approved for clinical use in both the United States and Europe.[43]

In common, echinocandins are not especially incredible substrates for CYP450 proteins (ie caspofungin is by far off the most CYP450-dependent echinocandin and anidulafungin has the smallest potential for interaction) and have little potential for drug–drug natural.

Measurement modification of caspofungin (and not of anidulafungin or micafungin) is provoked in cases of unpredictable hepatic work as chosen by the Child-Pugh score.[44] According to a precise summary of randomised controlled studies, the risk of DILI that does not lead to therapy discontinuation was 3.8 % for positive treatment (95 % CI: 2–5.5) and 8.7 % for echinocandins used for observational treatment (95 % CI: 6.4–11). The pooled risk for therapy discontinuation due to DILI was 3.7 % (95 % CI: 2.5-4.9) in unambiguous treatment regimens and 4.8 % (95 % CI: 3-6.5) in observational regimens. Patients on micafungin had a higher prevalence of DILI that needed withdrawal treatment (2.7 %, 95 % CI: 0.7-4.6) than those taking anidulafungin (0.8 %, 95 % CI: 0-2.3) or caspofungin (0.2 %, 95 % CI: 0.1-0.4).

Importantly, the echinocandin most closely associated with increasing liver proteins was caspofungin rather than micafungin. For example, the pooled DILI rates for caspofungin were 7 % (95 % CI: 4.1–9.9), micafungin was 3 % (95 % CI: 1–5.1) and anidulafungin was 2 % (95 % CI: 0.3–3.7) that did not come close to requiring cessation in the same consideration. The black-box warning may help prevent this from happening in the first place, and, if there is a necessary determined rise in ALT and/or AST

Flucytosine

Amphotericin B is commonly used to treat cryptococcal meningitis and invasive candidiasis in combination with flucytosine, a synthetic pyrimidine analogue. Hepatotoxicity, primarily seen as elevated transaminases, has been reported in as many as 41 % of people. Severe liver damage is rare but has been documented, especially with high dosages or prolonged treatment.

5-Fluorocytosine, an antimetabolite that was initially discovered in 1957, is a synthetic pyrimidine analogue specific to fungi that has antifungal effect against species of *Candida* and *Cryptococcus*. It does this by transforming into fluorouracil in sensitive yeast cells. The combination induction therapy of cryptococcal meningitis with DAMB is a well-known and repeatedly confirmed use of flucytosine. Additional applications Certain instances of tissue-invasive illness caused by *Candida species*.[4, 45] Hepatotoxicity, which shows up as a rise in hepatic transaminases, is the most frequent adverse effect of flucytosine. The definition of hepatotoxicity in different research is probably the reason why reports of hepatotoxicity vary from 0 % to 41 % of patients.[46] Although there have been reports of severe hepatic necrosis in two flucytosine-treated individuals with candidal endocarditis, the rise of liver function tests is usually modest to moderate and goes away

when the medication is stopped.[46] Particular interest are animal models which indicate a synergistic dose dependent inflammatory activation via the NF-κB pathway with the combination of amphotericin B and flucytosine.[47]

Allylamines

By inhibiting squalene epoxidase, the oral allylamine terbinafine interferes with the synthesis of ergosterol. Terbinafine undergoes extensive hepatic metabolism involving multiple cytochrome P450 isoenzymes. Hepatotoxicity caused by terbinafine can first present as cholestatic or hepatocellular injury and can occasionally progress to severe liver dysfunction, particularly in women or in individuals with underlying liver disease. The allylamines act by inhibiting squalene epoxidase in the fungal ergosterol biosynthesis pathway, causing squalene to accumulate to toxic levels and damaging the fungal cell.

Terbinafine (Lamisil® and various generics) is used orally to treat dermatophyte onychomycosis of the fingernails or toenails and *tinea capitis*.[48] Terbinafine is extensively metabolised by the liver, involving at least seven cytochrome P450 isoenzymes, and at least fifteen metabolites have been identified.[49] Hepatotoxicity is a recognised adverse effect of terbinafine, although the precise mechanism is not fully established. The liver injury appears to be idiosyncratic and immune mediated in some cases, as terbinafine or its metabolites have been shown to bind to hepatobiliary proteins and provoke an immune response. The early pattern of drug-induced liver injury can be hepatocellular or cholestatic, but it more commonly progresses to a cholestatic pattern that may be prolonged and can lead to vanishing bile duct syndrome.[50]

In a multicentre prospective study of DILI conducted from 1998 to 2007, drug-induced liver injury was an important cause of severe liver disease and showed a female predominance of 71 %. Of 1,198 patients with severe liver disease, 133 patients (11.1 %) had liver injury attributed to drugs; six of those cases were linked to antifungal agents, three of which were attributed to terbinafine.[51] A meta-analysis of oral antifungal safety in superficial dermatophytosis and onychomycosis estimated the pooled incidence of discontinuing terbinafine at 250 milligrams daily because of DILI to be 0.34 % (95 % CI: 0.09 to 0.60), compared with 0.70 % (95 % CI: 0.33 to 1.06) for itraconazole at 200 mg/day and 1.22 % (95 % CI: 0.00 to 5.30) for fluconazole at 50 mg/day.[52] In a later pharmacovigilance analysis of the United States Food and Drug Administration Adverse Event Reporting System covering 2004 to 2011, there were 1,964 reports of DILI. Terbinafine was the most frequently implicated drug, with 422 reports including 27 reports of liver failure; the reported odds of liver injury among terbinafine recipients were 3.39 (95 % CI: 2.32 to 4.96) times higher than among nonrecipients.[41]

Griseofulvin

Although it is less common than other antifungals, Griseofulvin, which is used to treat dermatophyte infections, is metabolised by hepatic enzymes and can cause liver damage. Patients who have hepatic failure should not use it.

Griseofulvin restrains parasitic microtubule assembly and has been utilised for verbal treatment of dermatophyte diseases for a few decades. The substance is trapped in the skin, hair and nails after attaching itself to keratin precursor cells. Griseofulvin undergoes oxidative demethylation, conjugates with glucuronic acid and is eliminated as metabolites in the urine and faeces. Specific liver-metabolised medications, including warfarin, cyclosporine and verbal contraceptives, have been shown to have increased clearance. Griseofulvin has become an auxiliary treatment for onychomycosis because of its lower survivability than terbinafine and itraconazole, however it is still an option for *tinea capitis*.[53] Griseofulvin has been linked to hepatotoxicity and patients who have hepatocellular dysfunction should not use this substance. Three children were stopped because of irregular hepatic chemicals (0.6 %), but no drug-related actual antagonistic events occurred in the 509 recipients of griseofulvin in the combined report of two randomised, controlled trials in children with *tinea capitis*. Two of 98 individuals who accepted griseofulvin showed increases in their AST and GGT levels, respectively, in a randomised, double-blind study that compared a 24-week course of terbinafine (250 mg/d) with a 48-week course of micronized griseofulvin (1000 mg/d) in 195

patients with onychomycosis.[54] In the universal FAERS database, three cases of liver damage, but no case of intense liver disappointment were detailed between 2004 and 2011, bookkeeping for the least announcing chances proportion for generally liver harm among all systemic antifungal specialists of 1.83 (95 % CI: 0.57–5.92).[41]

Hepatoprotective drug used in hepatotoxic antifungal agents

Some choices are utilised to control or prevent liver damage associated with hepatotoxic antifungal medications, even if there isn't a single, widely used hepatoprotective therapy exclusively for these drugs. One medication used to treat liver damage brought on by a variety of medications, including several antifungals, is N-acetylcysteine (NAC). In certain instances of DILI, glycyrrhizin and its derivatives are utilised due to its well-known hepatoprotective qualities.

NAC is a proven remedy for liver damage brought on by acetaminophen (paracetamol) overdose. It can also be used to treat hepatotoxicity from other medications, such as some antifungals. The National Institutes of Health (NIH) states that it functions by restoring glutathione, a chemical that aids in preventing damage to the liver.

Liquorice root contains a chemical called glycyrrhizin and its derivatives, such as glycyrrhizin acid, have hepatoprotective qualities. They are used to help shield the liver from harm and encourage healing in a variety of liver disorders, including DILI.

Expert opinions and future directions

IFDs remain a significant challenge, particularly among critically ill and severely immuno-compromised individuals. Despite advances in antifungal therapy, the management of these infections continues to be complicated by factors such as comorbidities, polypharmacy and pre-existing organ dysfunctions, particularly hepatic impairment. The availability of diverse antifungal agents, including triazoles, lipid-based amphotericin B formulations and echinocandins, has undoubtedly expanded treatment options, allowing for more personalised therapeutic approaches. However, hepatotoxicity associated with these agents remains a critical concern, especially in vulnerable patient populations like transplant recipients, intensive care patients and elderly individuals requiring long-term systemic antifungal therapy.

Among available antifungal classes, triazoles present the highest risk for hepatotoxicity, followed by terbinafine and amphotericin B formulations, while echinocandins exhibit a comparatively favourable hepatic safety profile. Although most hepatic adverse events associated with these drugs are mild to moderate and often reversible, there are reports of severe, life-threatening outcomes such as fulminant hepatitis and acute liver failure, particularly with voriconazole and other triazoles. The FAERS pharmacovigilance data further highlights the burden of antifungal-induced liver injury, with significant cases reported for commonly used agents like terbinafine, fluconazole and ketoconazole.

Despite existing data, there remains a pressing need for large-scale, well-designed post-marketing surveillance studies (phase IV trials) to comprehensively assess the real-world hepatotoxicity of antifungal agents across diverse patient populations. Current evidence is often derived from clinical trials with strict inclusion criteria, which may not reflect routine clinical scenarios involving multimorbid and polypharmacy patients. Robust, standardised pharmacovigilance systems are essential to capture the full spectrum and severity of antifungal-induced liver injury in these complex settings.

Moreover, the development and clinical validation of predictive biomarkers for the early detection of DILI represents a pivotal frontier in hepatology research. Emerging candidates such as high-mobility group box-1 (HMGB1) protein variants, microRNA-122 (miR-122) and cytokeratin-18 (K18) fragments show considerable promise in transforming the landscape of hepatotoxicity monitoring. These biomarkers offer the potential for earlier and more accurate identification of liver injury, allowing clinicians to implement timely therapeutic interventions and prevent progression to irreversible hepatic damage. Their integration into clinical practice could significantly enhance patient safety, particularly in the context of drug development and personalised medicine.

Genetic predisposition to antifungal-induced hepatotoxicity also warrants further exploration. The association between terbinafine-induced DILI and the HLA-A*33:01 allele exemplifies how pharmacogenomic screening could identify at-risk individuals prior to drug initiation. Expanding such research to other antifungal classes could significantly enhance patient safety and guide personalised antifungal therapy. In conclusion, while the current antifungal armamentarium offers greater flexibility and efficacy, vigilance regarding hepatotoxicity remains paramount. Future research must focus on real-world safety data, the integration of predictive biomarkers and pharmacogenomic profiling to optimise antifungal therapy while minimising the risk of hepatic complications. Overview of hepatic metabolism, elimination, dose adjustment and hepatotoxicity of antifungal agents as well as key results of DILI associated with antimycotics from FAERS Database 2004–2011 are presented in Table 1 and 2.

Table 1: Overview of hepatic metabolism, elimination, dose adjustment and hepatotoxicity of antifungal agents

Parameter	AMB	5-FC	FCZ	ITZ	VCZ	PCZ	AND	ISZ	CAS	MICA	GRI	TER
Hepatic metabolisation	–	–	+	+	+	+	+	–	+	±	+	+
CYP450 substrate	–	–	2C9, 3A4	2C9, 2C19, 3A4	2C9, 2C19, 3A4	3A4	3A4, 3A5	–	–	3A4	3A4	2C9, 1A2, 3A4, 2C8, 2C19
CYP450 inhibition	–	1A2, 2C9, 2C19, 2D6, 3A4	3A4	2C9, 2C19, 3A4	3A4	3A4, 2C8, 2C9, 2C19, 2D6	–	–	3A4	2D6	2D6	
Faecal elimination [% / % metabolised]	5–40	10 / 10	< 10	54–80 / 80	< 20	77 / –	46.1	30 / 10	35	40 / 71	36	
Urinary elimination [% / % metabolised]	5–20 / 40	90 / 5	90 / 10	20–35 / 20	80 / 78	14 / 14	45.5 / 1	1 / –	41 / 3	15 / 12	>70 / >70	
Dosage adjustment in hepatic impairment	–	–	–	±	+	–	–	–	+	–	+	
Hepatotoxicity	–	±	+	+	+	–	±	±	+	±	+	+
Liver failure reported	±	+	+	+	+	–	±	–	+	+	+	+

GRI: griseofulvin; 5-FC: flucytosine; VCZ: voriconazole; CAS: caspofungin; MICA: micafungin; ITZ: itraconazole; PCZ: posaconazole; AND: anidulafungin; AMB: amphotericin B; FCZ: fluconazole; TER: terbinafine;

Table 2: Key results: drug-induced liver injury (DILI) associated with antimycotics (FAERS database 2004–2011)

Pharmacological class	Active substance	Cases LI	Cases ALF	Cases OLI	ROR (95 % CI) LI	ROR (95 % CI) ALF	ROR (95 % CI) OLI
Polyenes (systemic)	Amphotericin B	251	4	265	5.33 (4.65–6.10)[1]	2.86 (1.69–4.84)[1]	5.20 (4.55–5.94)[1]
Imidazole derivatives	Miconazole[2]	16	-	16	0.33 (0.20–0.54)	-	0.30 (0.18–0.50)
Triazole derivatives	Ketoconazole[2]	88	6	94	6.68 (5.28–8.44)[1]	4.22 (1.88–9.45)[1]	6.64 (5.28–8.34)[1]

Triazole derivatives	Fluconazole	381	31	412	4.25 (3.81–4.74)[1]	3.46 (2.42–4.93)[1]	4.26 (3.83–4.73)[1]
	Itraconazole	178	4	182	3.73 (3.19–4.37)[1]	0.84 (0.32–2.25)	3.50 (2.99–4.09)[1]
	Voriconazole	342	19	361	5.61 (4.99–6.31)[1]	2.97 (1.89–4.67)[1]	5.48 (4.89–6.14)[1]
	Posaconazole	65	5	70	5.39 (4.12–7.04)[1]	4.00 (1.65–9.66)[1]	5.39 (4.16–6.99)[1]
Other antimycotics	Flucytosine	6	-	6	3.06 (1.31–7.13)[1]	-	2.80 (1.20–6.52)[1]
	Caspofungin	161	7	168	7.03 (5.90–7.37)[1]	2.79 (1.32–5.87)[1]	6.78 (5.71–8.05)[1]
	Micafungin	48	2	50	6.90 (5.02–9.49)[1]	-	6.64 (4.86–9.09)[1]
	Anidulafungin	13	1	14	4.97 (2.75–9.00)[1]	-	4.97 (2.79–8.84)[1]
Topical with systemic absorption	Griseofulvin[3]	3	-	3	2.00 (0.62–6.47)	-	1.83 (0.57–5.92)
	Terbinafine[3]	395	27	422	5.11 (4.58–5.69)[1]	3.39 (2.32–4.96)[1]	5.06 (4.55–5.62)[1]
Topical use, systemic potential	Nystatin	12	-	12	2.01 (1.12–3.62)[1]	-	1.84 (1.02–3.31)[1]
	Econazole	6	-	6	3.25 (1.39–7.60)[1]	-	2.97 (1.27–6.94)[1]
	Ciclopirox	3	-	3	3.39 (1.02-11.30)[1]	-	3.10 (0.93–10.33)

LI: liver injury; ALF: acute liver failure; ROR: reporting odds ratio; OLI: observed liver injury; FAERS database: US Food and Drug Administration Adverse Event Reporting System Database; 1-3: Grade 1 adverse events are mild and generally not bothersome. Grade 2 events are bothersome and may interfere with doing some activities but are not dangerous. Grade 3 events are serious and interfere with a person's ability to do basic things like eat or get dressed.

Although the amount and severity of the hepatic side effects seem to be minor, and there does not appear to be any dose dependency, the cumulative evaluation of the data suggests that therapy with amphotericin B may be linked to symptoms of drug-induced liver injury (DILI). The decreased incidence of amphotericin B deoxycholate (DAMB)'s hepatic side effects points to the influence of the lipid formulations' carriers, either directly or indirectly, through their enhanced accumulation of the parent in the liver. All the antifungal triazoles interact with the CYP450 enzyme system and are metabolised by the liver.[55] Despite the well-established risk of liver damage from antifungal triazoles, both clinical and experimental evidence point to a generally low incidence of more severe hepatotoxicity. Voriconazole is the only medication for which exposure-dependent hepatotoxicity has been demonstrated. Both cholestatic and hepatocellular damage can result from triazoles, and in rare instances, fulminant hepatitis with hepatic necrosis and severe liver failure have been seen. Although the liver metabolizes echinocandins, CYP450 enzymes[17] do not readily accept them as substrates. Several comparative clinical trials have revealed a favourable safety profile, and dose-escalation investigations with caspofungin and micafungin gave no indication for dose- or exposure-dependent liver impairment.[56] To put things in perspective, the FAERS pharmacovigilance database found that antifungal medicines were responsible for 1.964 DILI cases, or 2.9 % of all DILI cases. Of them, 112 individuals were classified as having liver failure (LF; 5.7 %). Terbinafine was responsible for the majority of DILI cases (n = 422; 27 with LF), followed by fluconazole (n = 412; 31 with LF), voriconazole (n = 361; 19 with LF), amphotericin B (all formulations; n = 265; 14 with LF), itraconazole (n = 182; 4 with LF), caspofungin (n = 168; 7 with LF), ketoconazole (n = 94; 6 with LF), posaconazole (n = 70; 5 with LF), micafungin (n = 50; 2 with LF), and anidulafungin (n = 14; 1 with LF). Ketoconazole users had the highest comparable reported odds ratios for liver failure (4.22; 95 % CI:1.88–9.45), followed by users of posaconazole (4.1.65–9.66), fluconazole (3.46; 2.42–4.93) and terbinafine (3.39; 2.32–4.96).[41]

Table 2 displays DILI instances linked to antimycotics that were submitted to the global FAERS database between 2004 and 2011. The degree of

observed or predicted toxicity, along with other disease and patient-related criteria, determines the influence of anticipated or observed hepatotoxicity on therapeutic decisions in clinical practice. Antifungal triazoles have the largest relative potential for hepatotoxicity, according to the information that is currently available. Terbinafine, amphotericin B compounds and echinocandins are next in line. The most typical situations where choosing the least hepatotoxic product may become important are individuals undergoing immunosuppressive treatments after obtaining a transplant, patients in the intensive care unit and maybe elderly patients with several comorbidities who need ongoing systemic antifungal medication in an ambulatory setting. Based on scant information, cross-reactions within a class may happen but are not always the result of interferences with hepatic activities; alternative agents within a class may also be a possibility. Large phase IV post marketing studies and standardised, reliable pharmacovigilance systems are obviously needed in the future to track and better understand the safety of antifungal medications in clinical settings. The creation of predictive biomarkers of DILI, such as cytokeratin-18 and its caspase-cleaved fragment, miR-122, or variations of the high-mobilitygroupbox-1 protein (HMGB1), may be a significant supplement to this. As evidenced by a recent study that linked terbinafine-induced DILI to the HLA A*33:01 gene, genetic vulnerability to DILI is also of great interest.[57] When combined, antifungal therapy is still difficult because of the possibility of side effects and drug interactions. In patients who are at high risk of developing hepatic dysfunction or who have underlying liver damage from previous or concurrent therapies, a comprehensive understanding of the metabolism and elimination of antifungal agents combined with safety information from clinical trials, post-marketing programs and pharmacodynamic studies may help guide the use of antifungal treatments.[58]

Conclusion

Antifungal therapy necessitates the careful selection of drugs with favourable hepatic safety profiles, especially in critically ill and immunocompromised patients. The compounds with the greatest potential to cause hepatotoxicity are azoles, terbinafine, amphotericin B formulations and echinocandins. To reduce the incidence of DILI, clinicians should use routine liver function monitoring, dose modifications in hepatic impairment and careful evaluation of drug interactions. Despite significant advancements in antifungal pharmacotherapy, the precise mechanisms driving hepatotoxicity remain incompletely understood. It is crucial to conduct further research on safer treatment alternatives and predictive biomarkers. Optimising patient safety still requires personalised antifungal stewardship that is informed by clinical judgment and pharmacovigilance.

Hepatotoxicity remains a pivotal concern in antifungal pharmacotherapy, particularly with triazoles and other systemically administered agents. As fungal infections often coexist with complex comorbidities and polypharmacy, clinicians must weigh therapeutic benefits against hepatic risks. Continuous liver function monitoring, individualised drug selection, dose adjustments in hepatic impairment and awareness of drug interactions are essential to mitigate DILI. With growing evidence linking antifungal agents to liver injury, future research must focus on elucidating precise hepatotoxic mechanisms and developing safer therapeutic strategies. Ultimately, personalised antifungal stewardship guided by pharmacovigilance and clinical judgment is imperative for enhancing patient safety.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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