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REVIEW

Multiresistant *Fusarium* Pathogens on Plants and Humans: Solutions in (from) the Antifungal Pipeline?

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Abstract: The fungal genus *Fusarium* contains numerous plant pathogens causing considerable economic losses. In addition, *Fusarium* species are emerging as opportunistic human pathogens causing both superficial and systemic infections. Appropriate treatment of *Fusarium* infections in a clinical setting of neutropenia is currently not available. ESCMID and ECMM joint guidelines, following the majority of published studies, suggest early therapy with amphotericin B and voriconazole, in conjunction with surgical debridement and reversal of immunosuppression. In this review, we elaborate on the trans-kingdom pathogenicity of *Fusarium*. Intrinsic resistance to several antifungal drugs and the evolution of antifungal resistance over the years are highlighted. Recent studies present novel compounds that are effective against some pathogenic fungi including *Fusarium*. We discuss the robust and dynamic antifungal pipeline, including results from clinical trials as well as preclinical data that might appear beneficial for patients with invasive fusariosis.

Keywords: *Fusarium*, trans-kingdom, novel compounds, antifungal pipeline, E1210, SCY-078, ASP2397, MGCD290, olorofim, AR-12, isavuconazole, efinaconazole, luliconazole

Trans-Kingdom Pathogenicity

Fusarium is a diverse genus of fungi containing several hundreds of species.[1–3] Some plant pathogenic members of the genus are restricted to a single host species, whereas others have a broad host range. Economic losses in agriculture may be considerable, and the genus is listed as one of the most destructive plant pathogenic fungi.[4,5] This genus is also frequently involved in vertebrate infection.[6,7] Although the conditions in host tissues of plants and animals are very different, nearly all 24 taxa that have been described to occur in human infections as real cases[8] have also been reported from plant diseases. *Fusarium* is capable of infecting plants as well as humans, a phenomenon known as trans-kingdom pathogenicity.[9] This unusual ability has been demonstrated in numerous studies.[10–18] *Fusarium oxysporum* f. sp. *lycopersici, F. keratoplasticum*, and *F. falciforme* are known for their pathogenicity to plants, but have also been reported from humans and other mammals.[11–13] Similarly, *F. pisi, F. temperatum, F. ramigenum, F. musae, Fusarium solani sensu stricto*, and *F. volatile* have been recovered from living plants, while also their clinical relevance has been underlined.[14,19–21] Cross-kingdom pathogenicity is in obvious conflict with plant host specificity. In *F. oxysporum*, small conditionally dispensable chromosomes carrying virulence factors, which are horizontally transmitted between germinating cells of different lineages in response to signals from a suitable habitat and which differentiate into infection hyphae,[22,23] may explain the sudden outbreaks observed in agricultural settings. Three

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Fusarium oxysporum mitogen-activated protein kinases (MAPKs) have distinct and complementary roles in stress adaptation and cross-kingdom pathogenicity.[24] Under selective pressure of host conditions, lineages show adaptation enhancing survival and replication. Segorbe et al[25] underlined the role of MAPK genes that contribute to the regulation of development, stress response and virulence in plants and animals. Instantaneous use of windows of opportunity is instrumental for rapid expansion. Van Baarlen et al noted a molecular similarity between hypothetical virulence factors in plant and human pathogens,[26] but among fungi in general such abilities are rarely combined[8] and thus cannot be generalized; more often, opportunism is combined with extremotolerance.[27] Cross-kingdom pathogenicity may thus be considered rather unique to *Fusarium*.

Fusarium oxysporum shows virulence in the *Galleria mellonella* infection model.[28] In humans, the infection mechanism is largely unknown. In general, immunocompromised individuals are highly susceptible to develop *Fusarium* disseminated infections, especially during neutropenia.[11,29,30] In otherwise healthy individuals, fusariosis generally remains a superficial infection;[31] the fungi are quite commonly isolated from dermatological samples in the tropics.[32] *Fusarium* keratitis, mostly initiated by traumatic inoculation of contaminated materials such as plant leaves,[19] is a major public health concern with an estimated global burden of about 1–1.2 million cases annually.[33]

Evolving Taxonomy

The taxonomy of the genus *Fusarium* has been affected by changes in species concept. During the last centuries, the number of recognized species by traditional taxonomists varied enormously, from as few as nine species to several hundreds.[34] In 1910, Apple and Wollenweber grouped all asexual fungi producing multicellular macroconidia with croissant shape from slimy sporodochia in *Fusarium*.[35] Wollenweber and Reinking used the differences in morphology to organize the genus into 16 sections. These sections contained 65 species, 55 varieties, and 22 host-specific formae on the basis of the color of stroma, the presence and absence of sclerotia, and the length and number of septations in macroconidia.[36] The characteristics used by those authors were the shape of conidia, microconidia, macroconidia, chlamydospores, basal foot cells and phialides. Also, the location of chlamydospores and other types of conidia was considered. Booth simplified this system to only 14 species.[37] The taxonomy proposed by Gerlach and Nirenberg was similar to that of Wollenweber and Reinking, recognizing 21 species.[38] Leslie and Summerell used morphological, biological and phylogenetic information for reclassification; they concluded that 70 species could be distinguished.[34] At present, with the dawn of molecular sequencing, more than 300 species are recognized, grouped in 22 species complexes, all differing in morphology, host association, and particularly in molecular parameters.[2] *Fusarium* was one of the first fungal groups where the term "species complex" was used for a series of closely related species. The term "species complex" has been defined,[8] elaborating on early papers for use in clinical routine by Chen et al[39] and Kwon-Chung et al,[40] as a monophyletic group which are different at the molecular epidemiological level but are functionally indistinguishable. In other words, there are identifiable discontinuities in their features, but the differences are not meaningful for practice. Variations or discontinuities may lead to reproductive barriers and speciation. Whether the speciation process has advanced sufficiently remains a matter of debate with every single species cluster.

Geiser et al brought together a consortium of clinical and phytopathological experts and launched a plea for nomenclatural stability with preservation of the name *Fusarium* for all clinically relevant species complexes.[41] The proposal was not effective, as Lombard et al moved the *F. solani* species complex to the genus *Neocosmospora*, and the *F. dimerum* species complex to a new genus *Bisifusarium*, on phylogenetic grounds.[42] As these genera include species with substantial significance as plant and human pathogens, transfers have not widely been accepted. However, the same research group recently reported that 68 species are accepted in the genus *Neocosmospora*, 29 of them described as new, while 13 new combinations were made and 11 species remained as yet undescribed.[43] For the sake of nomenclature stability in the clinical field, we adhere in this review to *Fusarium* as best known descriptor for fungi with morphological and ecological features in the sense of Wollenweber and Reinking,[36] as agents of "fusariosis."

Intrinsic Resistance to Antifungals

Most research on antifungals focuses on acquired resistance obtained by mutations in resistance genes, for example, the wealth of information available on *Aspergillus fumigatus* acquiring azole resistance triggered by exposure to agricultural antifungals in the environment.[44–47] Among agricultural fungicides, difenoconazole had the lowest activity against *Fusarium solani* SC with MICs of >32 mg/mL.[48] Herkert et al suggested a similar selective pressure on environmental *Fusarium* strains as that seen with *Aspergillus*.[48] However, natural, intrinsic resistance, which is independent of previous

antifungal exposure, has largely been neglected.[49] Some fungi are intrinsically resistant to single drugs (e.g., *C. krusei* to fluconazole or *C. lusitaniae* to amphotericin B), while others are resistant to different classes of antifungals (e.g., *C. auris*, some strains resistant to all antifungals).[50–52] Among the filamentous fungi, members of two adjacent orders are multiresistant, i.e., the Microascales (genera *Scedosporium, Lomentospora, Scopulariopsis*) and the Hypocreales (genera *Acremonium, Fusarium, Trichoderma*).[53] Discovery of genes conveying intrinsic resistance may not only provide drug targets for the development of new antifungals, but may also repurpose antifungals with limited effectivity by blocking the intrinsic drug resistance genes of the pathogens.[54]

Nearly all *Fusarium* species are among those fungi that have inherent structural and functional characteristics to resist antifungals without prior exposure. The reason why this phenomenon occurs naturally in *Fusarium* and other members of the above orders is unknown. Resistance has been observed for amphotericin B, itraconazole, fluconazole and echinocandins, but variable MIC results are recorded with the newer triazoles (posaconazole, voriconazole, and isavuconazole).[1] The molecular mechanisms of intrinsic resistance in *Fusarium* have not been described yet. However, a hypothetical molecular mechanism has been proposed by Fan et al who showed that CYP51 in *Fusarium* has three paralogues of sterol 14α-demethylase cytochrome P450 (CYP51A, -B, and -C), with CYP51C being restricted to *Fusarium*.[55] The same authors stated that CYP51A deletion increased the sensitivity of *Fusarium graminearum* to azoles.[55] Katiyar et al reported that mutations in the FKS1 gene,[56] i.e., amino acid substitutions P647A and F639Y in FKS1, contribute to intrinsic echinocandin resistance in *Fusarium solani*. The major mechanism responsible for high-level azole resistance in clinical species of *Candida* is overexpression of plasma membrane efflux pumps,[57] and this may also reduce azole susceptibility in *Fusarium*. Under the influence of azoles, various efflux mechanisms are triggered in *F. graminearum*, such as ATP-binding cassette (ABC) transporters to actively transport molecules across the cell membrane, reducing their impact on viability.[58] Experiments with the agricultural antifungal tebuconazole indicated the presence of different resistance mechanisms in *F. graminearum*. One of the phenotypes conveyed resistance to azoles, whereas another was related to multidrug resistance.[58]

Heteroresistance is another example of variation in drug susceptibility within a population. It was already reported that in *Candida albicans, Cryptococcus neoformans, Cryptococcus gattii, Aspergillus fumigatus* and *Aspergillus flavus,* single cells can give rise to progeny with heterogeneous resistance phenotypes resistant to the azoles.[59–61] This phenomenon may also be present in *Fusarium*.

Evolution of Antifungal Resistance

In recent decades, there has been much improper use of azoles, especially in agriculture. Resistance to azole fungicides in *Aspergillus fumigatus* as a human opportunist and *Mycosphaerella fijiensis* as a plant pathogen has been recognized during the last two decades, and the resistance mechanism is based on analogous genes (CYP51).[62,63] In 1997, the first azole-resistant clinical isolate of *Aspergillus fumigatus* was reported,[64] followed shortly thereafter by resistant *A. fumigatus* strains in the (agricultural) environment, exhibiting cross-resistance with fungicides.[65]

Due to the high fungicide pressure in the environment, resistance can also increase in *Fusarium*, although the main hypothesis is that resistance in *Fusarium* was already present prior to fungicide exposure. According to Lucas et al, in some organisms, the level of pre-existing resistance is high and should, therefore, be considered as intrinsic resistance.[66] In other organisms, processes such as increasing efflux pump activity or metabolism of toxins are not enough to confer intrinsic resistance to fungicides, but under high pressure of fungicides, resistance variation might occur.[67,68] In addition to the problem of intrinsic variation of drug susceptibility among *Fusarium* species, we need to add the emerging issue of acquired resistance (if present), which refers to the ability of *Fusarium* species to evolutionarily develop mechanisms that lower their susceptibility toward certain antifungals. In this scenario, *Fusarium*, as a plant pathogen, as well as *Aspergillus* species, which are saprobic on plant debris, all occur in the environment,[69] and therefore *Fusarium* is also exposed to the fungicides that are currently in use in agriculture. Consequently, it is useful to verify whether changes can be found in resistance profiles among clinical *Fusarium* isolates, in analogy to *Aspergillus*. We have checked this hypothesis by selecting *Fusarium* isolates from culture collections accessed before 1970 and after 1990 and tested their MICs against several antifungals including amphotericin B, itraconazole, posaconazole, voriconazole, isavuconazole, propiconazole, tebuconazole and difenoconazole using CLSI and EUCAST microdilution methods. We found that on the timescale and also comparing different methods, no statistically significant difference was revealed (p 0.122) between the MICs of strains from

before 1970 and strains isolated after 1990. However, strains of *Fusarium* differed among each other in MIC values (Tables 1 and 2),[1,70] showing that high MICs in *Fusarium* are strain specific. Current data show that some species/strains have higher MIC values than others. Our comparative antifungal susceptibility testing with clinical and environmental isolates from before 1970 and after 1990 showed that *Fusarium* indeed may have intrinsic resistance.

Current and New Drugs in the Pipeline

Here we discuss leading articles on antifungals that are available at present and those that are in the pipeline for use in patients with fusariosis (keratitis, onychomycosis and disseminated infections). The standard for treatment of keratitis due to *Fusarium* has not been determined, but is most commonly managed by topical application of natamycin or amphotericin B.[71] Natamycin was found to be active against *Fusarium* species both in vitro and in vivo, and recently it has been recommended in combination with voriconazole as the mainstay of treatment for *Fusarium* keratitis.[53] Early detection and installment of therapy are essential.[72] Voriconazole has been used in regimens combining topical (10 mg/mL eye drops) and oral (400 mg/day) administration, with good results, particularly when a hypopyon is present.[71] Recently, Oliveira et al and Kunt et al reported that chlorhexidine demonstrated in vitro antifungal activity against *Fusarium* strains isolated from keratitis lesions.[73,74] Todokoro et al demonstrated that luliconazole exhibited strong in vitro antifungal activity against a broad range of filamentous fungi including *Fusarium* species.[75]

Combination therapy of natamycin with voriconazole, itraconazole or micafungin showed synergism,[76] although Prajna et al reported in a clinical trial equal or inferior efficacy of 1% voriconazole compared to 5% natamycin alone in eye drops.[77] Rees et al evaluated in vitro activities of natamycin and voriconazole in combination with four non-antifungal ophthalmic agents (5-fluorouracil, dorzolamide, EDTA and timolol).[78] In eight *Fusarium* ocular isolates, resistance was noted to both natamycin and voriconazole. The data suggested that commonly used ophthalmic agents enhance the in vitro activity of antifungal drugs against drug-recalcitrant ocular fusariosis when used in combination.[78] Posaconazole and ravuconazole are new azoles that have yet to be topically applied in ophthalmic settings.

Therapeutic outcomes of *Fusarium* onychomycoses, particularly of subungual cases, are variable. No standard treatment of onychomycosis due to *Fusarium* has as yet been identified. In general, itraconazole is applied either daily or intermittently.[71] A second commonly used drug is terbinafine, sometimes combined with topical ciclopirox and amorolfine lacquer or with keratolytics such as urea.[79,80] Tupaki-Sreepurna et al presented susceptibility profiles of 44 common nondermatophyte fungi including *Fusarium* against efinaconazole and showed excellent in vitro activity.[81] Luliconazole and lanoconazole are new imidazole antifungal agents with broad-spectrum antifungal activity used clinically as topical drugs in the treatment of onychomycosis and dermatophytosis.[82] Abastabar et al concluded that luliconazole, lanoconazole and efinaconazole exhibit potent in vitro activity against clinical and environmental *Fusarium* species, and these compounds might be an option for treating onychomycosis due to *Fusarium*.[83] The same authors reported that the in vitro antifungal activity of efinaconazole, with a GM MIC of 0.85 μg/mL, was superior to that of amphotericin B, natamycin, other triazoles and echinocandins.[83]

Despite advances in therapy and early diagnosis, invasive fusariosis remains associated with high morbidity and with up to 70% mortality in case of dissemination.[84] Research results confirm a high level of resistance, regardless of the species or strain of *Fusarium* involved. The high MIC levels are worrying and are imperative for the development of new drugs. The prognosis of patients with disseminated fusariosis is poor and is mainly associated with reversal of neutropenia, but novel antifungals and formulations may improve outcomes also.[49] Isavuconazole has MICs against *Fusarium* species that are equivalent to or higher than other triazoles (1 to ≥16 μg/mL).[69,85] In two clinical trials (SECURE and VITAL), seven patients with disseminated fusariosis were treated with isavuconazole as primary therapy, resulting in 44% 90-day survival.[86,87]

Fusarium antifungal resistance remains a significant problem for patients with compromised immunity and at high risk for invasive infection, and therefore there is an urgent need for novel therapeutic compounds and strategies. The following drugs are in the pipeline and have been studied and investigated in phase 1–2 preclinical trials (Table 3). ASP2397 is a new antifungal compound, producing its antifungal effects by disruption of the intracellular membrane. It has a modest in vitro antifungal activity (≤8 μg/mL) against *Fusarium* species.[88] AR-12 (celecoxib derivative) has shown antifungal activity against different fungi such as *Cryptococcus*

Table 1 GM, MIC Range, MIC_{50} and MIC_{90} Va/Lues (μg/mL) Obtained by Antifungal Testing of Amphotericin, Itraconazole, Posaconazole, Voriconazole, Isavuconazole, Propiconazole, Tebuconazole and Difuconazole of 38 (Clinical and Environmental *Fusarium* Isolates) Isolated Before 1970

Fungus (Number)	Antifungals	Test Method	Number of Isolates at MIC (mg/L)													MIC_{50}	MIC_{90}	GM
			<0.031	0.031	0.063	0.125	0.25	0.5	1	2	4	8	16	32	>32			
Fusarium species (38) before 1970	Amphotericin B	CLSI		1		3	3	5	19	5		1			1	1	2	0.82
		EUCAST				1	3	2	9	17	1	3	1		1	2	8	1.64
	Itraconazole	CLSI				1									37	>32	>32	54.31
		EUCAST				1									37	>32	>32	54.31
	Posaconazole	CLSI			1	1	2		2		1				31	>32	>32	24.79
		EUCAST					3	1	3	1					31	>32	>32	23.90
	Voriconazole	CLSI				1	1	2	1	3	7	14	7	1	1	8	16	5.26
		EUCAST						3	1	3	4	13	3	4	7	8	>32	9.09
	Isavuconazole	CLSI					2		2	2		4	17	6	5	16	>32	12.39
		EUCAST						3	1	1	1	2	3	14	13	32	>32	20.66
	Propiconazole	CLSI						2	2	1	2		1	6	24	>32	>32	27.16
		EUCAST						1	2	2	2			3	28	>32	>32	30.85
	Tebuconazole	CLSI					1	1	1	3		5	5	15	7	32	>32	16.00
		EUCAST						1	2	2	2		2	9	20	>32	>32	25.24
	Difuconazole	CLSI						1	2	2	2		1	5	25	>32	>32	28.68
		EUCAST						1	1	2	2	1		3	28	>32	>32	33.19

Table 2 GM, MIC Range, MIC_{50} and MIC_{90} Values (μg/Ml) Obtained by Antifungal Testing of Amphotericin B, Itraconazole, Posaconazole, Voriconazole, Isavuconazole, Propiconazole, Tebuconazole and Difuconazole of 82 (Clinical and Environmental *Fusarium* Isolates) Isolated After 1990

Fungus (Number)	Antifungals	Test Method	Number of Isolates at MIC (mg/L)													MIC50	MIC90	GM
			<0.031	0.031	0.063	0.125	0.25	0.5	1	2	4	8	16	32	>32			
Fusarium species (82) after 1990	Amphotericin B	CLSI					2	20	33	21	4	1			1	1	2	1.13
		EUCAST						1	20	32	13	11	3		2	2	8	2.62
	Itraconazole	CLSI													82	>32	>32	64.0
		EUCAST												1	81	>32	>32	63.5
	Posaconazole	CLSI					1			1					80	>32	>32	57.3
		EUCAST							1					1	80	>32	>32	60.3
	Voriconazole	CLSI						1		2	26	25	25	2	1	8	16	7.87
		EUCAST						1		1	8	19	17	8	28	16	>32	19.1
	Isavuconazole	CLSI						2			2	14	19	21	24	32	>32	22.6
		EUCAST								1		5	12	16	48	>32	>32	38.5
	Propiconazole	CLSI							1	1	1	3	10	8	58	>32	>32	41.2
		EUCAST								2		1	2	6	71	>32	>32	52.6
	Tebuconazole	CLSI							1	1	2	11	16	19	32	32	>32	26.8
		EUCAST							1			3	5	11	62	>32	>32	47.2
	Difuconazole	CLSI								2		2	12	10	56	>32	>32	41.9
		EUCAST									1		1	11	69	>32	>32	55.4

Table 3 Antifungal Product Type in the Pipeline, Pathogen, Phase of Clinical Trial and Expected Activity Against *Fusarium*

Pathogen	Compound (Notes)	Company	Development Status	Antifungal Class	Activity (MIC µg/mL)	Related Ref.s
Fusarium	Isavuconazole	Astellas Pharma, US, Inc. – License holder Basilea Pharmaceu., Switzerland – outside USA and Canada	FDA approves new antifungal drug Cresemba (Oral/IV) March 6, 2015	Triazole	Variable from 1 to ≥16	70
	Efinaconazole (KP-103)	JUBLIA® Valeant Pharmaceu., Canada	FDA approval: September 2014 Topical 10%	Triazole	0.85	83
	Luliconazole (NND-502)	Nihon Nohyaku Co Ltd (Osaka, Japan)	Approved, USA, Nov 15, 2013 Cream 1%, solution 10%	Imidazole	0.005	83
	Lanoconazole	Nihon Nohyaku Co Ltd (Osaka, Japan)	Approved, USA, Nov 15, 2013 Cream 1%, solution 10%	Imidazole	0.013	83
	AR-12 celecoxib derivative	Arno Therapeutics, Flemington, NJ, USA)	-	Celecoxib Derivative	4	89
	F901318 = Olorofim	F2G, Manchester, UK	Phase 2 Preclinical	Orotomides	1 to 2	93
	E1210 Inositol acyltransferase inhibitor Oral	Eisai Co., Japan	Preclinical	-	−0.015–0.25 -0.12	94
	SCY078 (formerly MK-3118) IV/Oral	Scynexis, Durham, NC, USA	Phase 2	Triterpene/ Enfumafungin derivative	poor activity	97
	T-2307 Arylamidine derivatives	Toyama, Japan	Preclinical	Arylamidine derivatives	0.125	99
	MGCD290 Oral histone deacetylase inhibitor	Mirati Therapeu., CA, USA	Phase 2	Hos2 histone deacetylase inhibitor	Effective in combination	101

neoformans, Candida albicans and *Scedosporium* species and was active against *Fusarium* species at a MIC of 4 μg/mL.[89,90] F901318 (olorofim, F2G) is a member of a novel class of antifungals, the orotomides, acting by interference of pyrimidine biosynthesis in the fungal cell. This compound displayed excellent activity against a broad range of pathogens.[91] It has been used as an intravenous and oral agent for use in systemic mold infections.[92] However, olorofim was tested against *Fusarium* species with variable results.[93] Full inhibition was achieved with *F. proliferatum* (MIC 0.016 μg/mL), 50% inhibition with *F. solani* (MIC 1–2 μg/mL), while no inhibition was observed with *F. dimerum*.[93] APX001 (E1210/1211, fanmogepix) is an antifungal compound that is still under development.[92] Reportedly, it has potent in vitro antifungal activity against molds that are difficult to treat, such as *Fusarium*, where MIC values of 0.015–0.25 μg/mL[94] and 0.12 μg/mL[95] were obtained. The arylamidine enfumafungin (MK-3118, SCY-078, ibrexafungerp) is a novel, orally bioavailable 1,3-β-d-glucan synthesis inhibitor. The compound was highly active against multidrug resistant *Candida albicans* and *C. glabrata* isolates,[96] but showed no or poor activity against *Fusarium* species.[97] However, the molecular variation SCY-078 T-2307 that inhibits fungal growth by interference with cellular metabolism[98,99] has potent in vitro activity (0.125 μg/mL) against *Fusarium solani*.[100] The histone deacetylase 2 inhibitor MGCD290 is effective in combination with both azoles and echinocandins in vitro and in animal models.[101,102] The combination with voriconazole demonstrated synergy against six out of eight *Fusarium* isolates.[101]

In conclusion, *Fusarium* is one of the few fungi capable of infecting plants as well as humans, a phenomenon known as trans-kingdom pathogenicity. Intrinsic resistance and acquired resistance of *Fusarium* species are a threat to both human medicine and agriculture. Especially immunocompromised patients with longstanding neutropenia and disseminated fusariosis have a poor prognosis. Reversal of neutropenia is life-saving, but new classes of antifungals in the pipeline may improve the outcome of these severe opportunistic infections.

Disclosure

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