ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2024 June 6; 12(16): 2686-2916

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

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PUBLICATION DATE
June 6, 2024

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World Journal of Clinical Cases

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World J Clin Cases 2024 June 6; 12(16): 2686-2691

DOI: 10.12998/wjcc.v12.i16.2686

ISSN 2307-8960 (online)

EDITORIAL

Antifungal pipeline: Is there light at the end of the tunnel?

Georgios Schinas, Nikolaos Spernovasilis, Karolina Akinosoglou

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Mohapatra S, India

Received: December 11, 2023
Revised: March 19, 2024
Accepted: April 19, 2024
Published online: June 6, 2024

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Abstract

The misuse and overuse of classic antifungals have accelerated the development of resistance mechanisms, diminishing the efficacy of established therapeutic pathways and necessitating a shift towards alternative targets. Despite this pressing need for new treatments, the antifungal drug pipeline has been largely stagnant for the past three decades, primarily due to the high risks and costs associated with antifungal drug development, compounded by uncertain market returns. Extensive research durations, special patient populations and rigorous regulatory demands pose significant barriers to bringing novel antifungal agents to market. In response, the "push-pull" incentive model has emerged as a vital strategy to invigorate the pipeline and encourage innovation. This editorial critically examines the current clinical landscape and spotlights emerging antifungal agents, such as Fosmanogepix, Ibrexafungerp, and Olorofim, while also unraveling the multifaceted challenges faced in new antifungal drug development. The generation of novel antifungals offers a beacon of hope in the battle against antimicrobial resistance, but it is premature to declare them as definitive solutions. Their future role hinges on thorough clinical validation, cost-effectiveness assessments, and continuous post-marketing surveillance. Only through strategic implementation and integration with market strategies we can transform the landscape of antifungal development, addressing both the resistance crisis and the treatment challenges.

Key Words: Antifungals; Resistance; Fosmanogepix; Ibrexafungerp; Olorofim

Core Tip: The landscape of antifungal therapy has long been dominated by a handful of drug classes, namely azoles, polyenes, and echinocandins. Issues such as the development of resistance/tolerance, interactions and inherent toxicity, and narrow spectrum of activity have limited their therapeutic utility to clinicians. All these limitations underline the urgent need for novel approaches, with the pipeline for new antifungals having been relatively dry for about 30 years. Thankfully, the pharmaceutical landscape has recently shown promising signs of innovation regarding antifungal agents.

Citation: Schinas G, Spernovasilis N, Akinosoglou K. Antifungal pipeline: Is there light at the end of the tunnel? *World J Clin Cases* 2024; 12(16): 2686-2691
URL: https://www.wjgnet.com/2307-8960/full/v12/i16/2686.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i16.2686

INTRODUCTION

While traditionally considered as secondary to bacterial and viral infections in both prevalence and severity, fungal infections have emerged as a significant global health threat[1]. Invasive fungal infections, in particular, have long been a subject of concern, but recent years have seen an alarming increase in both their incidence and complexity[2,3]. This newfound prominence may be attributable to multiple factors, including climate change, the increasing number of immunocompromised patients, advancements in medical interventions that disrupt normal flora, and the misuse of antifungal agents in certain settings, including agriculture, all of which create an environment fit for fungal proliferation, spread, and genetic evolution[4].

The escalating issue of antifungal resistance has further exacerbated the situation[5]. Most prominently the global spread of multidrug resistant strains of *Candida glabrata* and *Candida auris*, as well as the concurrent emergence of azole-resistant *Aspergillus* infections, have raised the stakes in the ongoing battle[6]. The emergence of these strains is not merely a regional concern but a global phenomenon, affecting both developed and developing nations[7]. *Candida auris*, for example, which was first identified in 2009 in Japan, has been responsible for numerous outbreaks in healthcare settings all around the world ever since[8]. Notably, it has exhibited increasing resistance to all three major classes of antifungals, significantly complicating hospitalizations and treatment outcomes[9]. According to the most recent estimates from the United States, this has led to associated mortality rates of up to 34%[10].

Despite the grim outlook and the heightened interest in the development of new antifungals, the existing armamentarium remains limited. Many of the antifungal agents in current use were developed decades ago and are rapidly losing their relevance in modern-day clinical practice, spurring the question: Is there light at the end of the tunnel for antifungal therapy?

THE CURRENT STATE OF AFFAIRS

The landscape of antifungal therapy has long been dominated by a handful of drug classes, namely azoles, polyenes, and echinocandins. While these agents have been effective in treating a wide range of fungal infections, their limitations are becoming increasingly apparent. Issues such as the development of resistance/tolerance, interactions and inherent toxicity, and a narrow spectrum of activity have limited their therapeutic utility to clinicians[11,12]. Indeed, the most commonly employed antifungal agents, *i.e.*, azoles and echinocandins, have shown declining efficacy due to widespread resistance[13,14] and limited clinical usage owing to their severe adverse effects, *e.g.*, hepatotoxicity, nephrotoxicity and drug-drug interactions, making them less viable for long-term or combination options[12,15].

The challenge that antifungal infections pose is further compounded by the limited diagnostic tools available for early identification of fungal infections and resistance patterns. Conventional culture-based methods are especially time-consuming and may not be sensitive enough to detect emerging strains or identify resistance mechanisms. Molecular diagnostic tools, such as polymerase chain reaction, offer a reliable alternative in a variety of different scenarios. However, despite their increasing use and validation in certain contexts, these methods are not yet universally available or integrated into routine clinical practice for all fungal infections[4].

All these limitations underline the urgent need for novel approaches. With the pipeline for new antifungals having been relatively dry for about 30 years[16], the medical community is keenly awaiting the next generation of antifungal agents that can address the limitations of existing therapies and offer new avenues for treating resistant and novel fungal strains.

NEW KIDS ON THE BLOCK: INNOVATIVE AGENTS

The pharmaceutical landscape has recently shown promising signs of innovation regarding antifungal agents. Recent advances in genomics and drug design have paved the way for the development of novel therapeutic targets, employing new mechanisms of action. Several promising drugs are currently in various stages of development, each with unique

features that make them potential game-changers in antifungal therapy. Fosmanogepix, Ibrexafungerp, and Olorofim are among the most promising.

Fosmanogepix, which targets the Gwt1 enzyme, that is involved in the glycosylphosphatidylinositol biosynthetic pathway, has shown efficacy against a broad range of fungal pathogens, including multidrug-resistant strains. The recently published Phase 2 results indicate that Fosmanogepix is effective and well-tolerated for the first-line treatment of candidemia in non-neutropenic adults with a treatment success rate of 80% and an impressive 85% survival rate at 30 d follow-up[17]. Notably, approximately 48% of patients were transitioned to oral Fosmanogepix, indicating its potential for flexible administration. The ongoing Phase 3 trial aims to investigate the efficacy and safety of Fosmanogepix, compared to standard antifungal treatment, *i.e.*, caspofungin and fluconazole, in adults with candidemia and/or invasive candidiasis.

Ibrexafungerp, a first-in-class triterpenoid antifungal, has completed Phase 3 trials, becoming the first non-azole agent approved by the United States Food and Drug Administration (FDA) for treating vaginal yeast infections caused by *Candida* spp., and is currently under investigation for invasive pulmonary aspergillosis (in combination with voriconazole-SCYNERGIA trial) and invasive candidiasis (echinocandin followed by either ibrexafungerp or voriconazole-MARIO trial)[18].

Olorofim, another novel agent, targets rare mold infections by inhibiting dihydroorotate dehydrogenase in the pyrimidine synthesis pathway[18]. Of note, it has exhibited a favorable pharmacokinetic profile that allows for oral administration. It has been granted Qualified Infectious Disease Product and Breakthrough Therapy Designations for various invasive fungal infections from the FDA and according to the latest release from the drug sponsor, detailing the key findings of the Phase 2b open-label study, Olorofim demonstrated an acceptable benefit-risk profile with an overall success rate of 28.7% at day 42 and 27.2% at day 84 of follow-up. The all-cause mortality rates were 11.4% at day 42 and 15.8% at day 84 and the drug was generally well-tolerated, even in extended therapy exceeding 2 years[19]. A global Phase 3 trial is currently underway to compare treatment with Olorofim *vs* amphotericin B in patients with invasive aspergillosis[20].

Rezafungin, branded as Rezzayo, also deserves an honorable mention, despite its already established mechanism of action, as it was approved by the FDA on March 2023 for treating candidemia and invasive candidiasis in adult patients, particularly those with limited or no alternative treatment options. Its rather long half-life of approximately 133 h allows for less frequent intervals between doses, setting the basis for a once-weekly treatment regimen[21].

While these agents show considerable promise, it is essential to approach their potential with cautious optimism. The rigorous pharmacological evaluation, long-term safety data, and real-world effectiveness studies are yet to be conducted. Their true potential can only be assessed after extensive clinical trials that evaluate not just their efficacy but also their safety, tolerability, and cost-effectiveness.

CHALLENGES AND CONSIDERATIONS OF THE PIPELINE DEVELOPMENT

While the development of new antifungal agents is certainly encouraging, it is crucial to acknowledge the myriad challenges and considerations that accompany their journey from the laboratory to clinical use. From early-stage research to clinical trials and regulatory approvals, the path to bringing a new antifungal agent to market is full of financial and logistical hurdles. The differences in legislations and regulatory approval processes between the United States and Europe add another layer of complexity for developers seeking global market entry.

However, common ground exists in that both the FDA and the European Medicines Agency (EMA) have stringent requirements for the approval of new antimicrobial agents. These requirements include not only extensive pre-clinical and clinical data on efficacy and safety but also post-marketing surveillance to monitor for adverse effects and the emergence of resistance. The rigorous nature of these requirements extends the drug development timeline and increases the financial burden, exceeding 10 years and $300 million according to some estimates[22], thereby acting as a deterrent for pharmaceutical companies.

Designing and conducting clinical trials for antifungal agents, in particular, presents unique challenges, primarily due to logistical considerations and the need for appropriate endpoints. To begin with, the relative rarity of certain invasive fungal infections necessitates multi-center trials to achieve adequate sample sizes[23]. Furthermore, the diversity of fungal pathogens' resistance patterns, the varying patient populations affected, and the different anatomical site of infection requires a multifaceted approach in trial design[24]. Ethical considerations, such as the use of placebo controls and/or other comparators, are especially complex due to the life-threatening potential of MDR strains and invasive species. What's more, the selection of clinically meaningful endpoints, like all-cause mortality or time to clinical resolution, is a point of contention among researchers, complicating direct comparisons of the efficacy of new agents. Lastly, the question of accessibility cannot be overlooked. Even if a new antifungal agent proves to be effective and gains regulatory approval, its impact will be limited if it is not readily accessible to all patient populations. This includes not only financial accessibility but also the availability of the drug in various healthcare settings, from large hospitals to rural clinics.

"PUSH AND PULL" INCENTIVES: CATALYZING RESEARCH AND DEVELOPMENT

It is becoming increasingly evident that antifungal drug development is unattractive from an investment standpoint, particularly for large pharmaceutical companies. Over the past three decades, there has been a notable decline in the

number of major pharmaceutical firms investing in antimicrobial research and development. Today, only about five companies maintain a significant investment in this area[25]. This reduction reflects the high risks and costs associated with drug development, compounded by the uncertain financial returns in the antimicrobial market.

In this challenging landscape, the concept of "push-pull" commercial incentives emerges as a strategy to facilitate the development and market entry of new treatment agents[26]. "Push" incentives, primarily provided by government and non-profit organizations, aim to stimulate early-stage research and development. These incentives can include funding, grants, and infrastructural support, helping to alleviate the financial risk associated with the initial stages of drug discovery and development. Among the most prominent examples of these incentives is the work done by Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator, a global non-profit partnership dedicated to accelerating antibacterial research. Other significant contributors include the Innovative Medicines Initiative in Europe, which collaborates with various stakeholders to accelerate the development of, and access to, innovative medicines. In the United States, the National Institute of Allergy and Infectious Diseases plays a similar role, offering grants and funding opportunities aimed at advancing research in infectious diseases, including antifungal resistance.

On the other hand, "pull" incentives, often implemented by regulatory bodies like the FDA and EMA, focus on creating a viable market for new drugs. These can include extended market exclusivity, patent extensions, and fast-track approval processes, which are designed to ensure a return on investment once the drug reaches the market. In the United States, for example, the Generating Antibiotic Incentives Now Act provides additional incentives such as the Qualified Infectious Disease Product Designation, offering extended exclusivity periods for drugs that target severe or life-threatening fungal infections[27]. Additionally, streamlined approval pathways are in place for antifungals intended for use in a limited and specific population of patients (limited population pathway). The European Union's approach emphasizes a unified procedure for drug approval and stresses multi-national collaboration. This strategy is beneficial for "pushing", *i.e.*, facilitating clinical trial conduction, while aligning with the "pull" aspect by facilitating market entry across multiple nations.

Together, these "push-pull" mechanisms create an environment that not only encourages the development of new antifungal drugs but also ensures their sustainability and accessibility post-approval. Figure 1 illustrates the journey of a drug from initial research through to market entry, highlighting the role of "push" incentives (yellow) in overcoming early-stage development challenges and "pull" incentives (green) in ensuring market viability and return on investment.

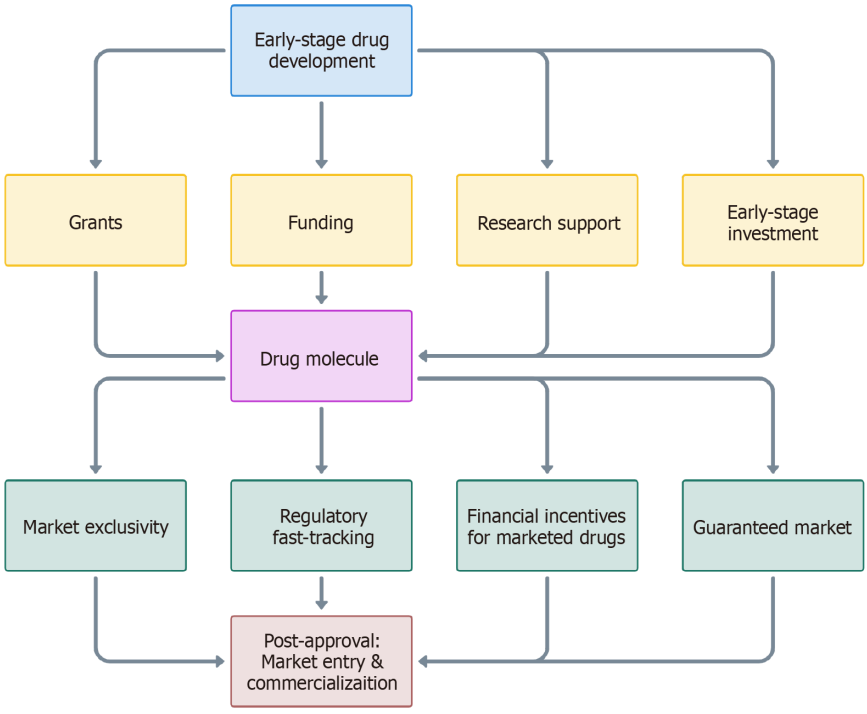

Figure 1 "Push-pull" incentives in antifungal drug development.

CONCLUSION

As we stand at the turning point of a new era in antifungal therapy, the question remains: Is there light at the end of the tunnel? While the development of promising new antifungal agents offers a glimmer of hope, it is crucial to temper our optimism with a realistic appraisal of the challenges ahead.

It is important to note that the success of these new agents cannot be gauged solely by their efficacy in clinical trials. Their real-world effectiveness must be rigorously evaluated through post-marketing surveillance and long-term follow-up studies, monitoring not only therapeutic outcomes but also adverse effects, drug-drug interactions, and the possible emergence of resistance. In addition, their potential clinical applications remain to be seen, as they are yet to be studied in

diverse patient populations.

Moreover, the sustainability of these new antifungal therapies must be considered. While they may offer innovative mechanisms of action that circumvent existing resistance pathways, their long-term impact will be determined by their accessibility and the stewardship programs that accompany their use. Without robust antifungal stewardship programs and responsible prescribing practices, even the most promising new agents risk becoming another chapter in the story of failed therapies.

In conclusion, while the new candidates in the antifungal pipeline present innovative approaches to a complex and growing problem, they are not a panacea. They represent pieces of a much larger puzzle that includes not only drug development but also early diagnosis, comprehensive treatment plans, and global health policies. As we move forward, a multidisciplinary approach that involves clinicians, researchers, and policymakers will be crucial to fully illuminating the path ahead in the battle against fungal infections. By effectively leveraging existing incentives, we can better navigate the complexities of drug development, addressing both the pressing need for new antifungal agents and the practical realities of bringing these drugs to market. This approach not only stimulates innovation but also aligns with global health priorities, potentially transforming the landscape of antifungal therapy.

FOOTNOTES

Author contributions: Schinas G, Spernovasilis N and Akinosoglou K contributed to the review of literature, writing and editing of the manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest.

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S-Editor: Zheng XM
L-Editor: A
P-Editor: Zhao S

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