Scientific Research Publishing

Open Journal of Ophthalmology, 2024, 14, 1-7
https://www.scirp.org/journal/ojoph
ISSN Online: 2165-7416
ISSN Print: 2165-7408

Advances in Drug Treatment of Fungal Keratitis

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How to cite this paper: Wu, X.R. and Wang, J.H. (2024) Advances in Drug Treatment of Fungal Keratitis. *Open Journal of Ophthalmology*, **14**, 1-7.
https://doi.org/10.4236/ojoph.2024.141001

Received: November 5, 2023
Accepted: December 26, 2023
Published: December 29, 2023

Abstract

Fungal keratitis is an important cause of corneal blindness in China, accounting for 45% of infectious keratitis. The main pathogenic bacteria include yeast, filamentous bacteria and nearly 100 kinds of fungi, which are difficult to diagnose, difficult to treat and poor prognosis. When the infected fungal strains have strong virulence and poor drug sensitivity, it is easy to prolong the disease. Once the fungal infection involves the whole limbus and reaches the whole layer of the cornea, it will be followed by intraocular tissue infection such as anterior chamber, lens and vitreous body. When the infection is difficult to control and the visual function is seriously damaged, the enucleation of eye contents has to be performed, which causes irreversible harm to the patient's appearance and physical and mental health. Therefore, in order to gain greater hope for the vision of patients with fungal keratitis, In recent years, with the continuous progress of clinical medicine and microbiological diagnostics, the treatment methods of fungal keratitis have been constantly updated. This article will briefly review the new progress in drug and surgical treatment of fungal keratitis in recent years to provide patients with better visual prognosis.

Keywords

Fungal Keratitis, Treatment

1. Introduction

Fungal keratitis is one of the infectious keratopathy, which has a high rate of blindness and is mostly caused by plant trauma. Patients often have symptoms such as eye pain, jealousy, photophobia, foreign body sensation, blurred vision, and so on. The disease is difficult to diagnose, difficult to treat and poor prognosis, which seriously threatens the vision of patients. In developing countries,

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fungal keratitis ranks second in infectious keratitis, while in a large agricultural country like China, it ranks first, which is an important cause of corneal blindness in China, so it is highly concerned by ophthalmologists [1]. At present, drug therapy is still the main clinical treatment of fungal keratitis, but there are many problems in the existing commercial ophthalmic antifungal drugs, such as scarcity of kinds, weak corneal permeability, low biocompatibility, obvious ocular surface irritation and strong drug resistance. It brings great challenges to clinical treatment [2]. When corneal perforation is serious, keratoplasty is needed. Although keratoplasty can remove the focus of infection more quickly and restore the anatomical integrity of corneal tissue than drug treatment, there is a shortage of corneal donors in our country at present. It is difficult to meet the needs of surgical treatment, resulting in many patients can only remove the eyeball and lose the vision of the affected eyes for life. Therefore, experts and scholars unanimously recommend following the principles of early diagnosis and early treatment, retaining more vision for patients as much as possible, and focusing on improving the efficacy of drugs to avoid the dilemma of having to undergo surgical treatment. Therefore, this paper summarizes the progress of drug treatment of fungal keratitis in recent years, so that clinicians can choose the best drugs for the treatment of fungal keratitis and strive for more opportunities for the recovery of patients' visual acuity.

2. General Antifungal Drugs

2.1. Polyenes

Polyene drugs are the most widely used antifungal drugs in clinic at present, which combine with ergosterol on fungal cell membrane. by changing the permeability of the cell membrane to intracellular potassium ions, amino acids, nucleotides and other important substances to destroy the normal metabolism of cells and inhibit fungal growth. The main representative drugs are 5% natamycin eye drops and 0.1% - 0.2% amphotericin B. Natamycin is the only broad-spectrum antifungal drug approved by FDA in the United States. This eye drop is easy to attach to the surface of corneal ulcer. It not only has a high local drug concentration, but also can be retained for a long time. Natamycin can gradually penetrate into the corneal parenchyma and give full play to its efficacy. Eye treatment is tolerable and non-toxic. However, because it is insoluble in water, 5% suspension eye drops are used clinically [3]. Amphotericin B has strong activity against Aspergillus and Candida, but the main pathogen of fungal keratitis in China is Fusarium. Amphotericin B is ineffective in the treatment of this bacteria.

2.2. Triazoles

Triazole drugs mainly inhibit the growth of fungi through the lack of ergosterol synthesis, which is the structural and functional component of fungal cell membrane. The representative drugs are itraconazole, fluconazole and voriconazole. Itraconazole is the first synthetic azole drug with antibacterial activity against

both filamentous bacteria and yeast, especially sensitive to Aspergillus, but its hepatotoxicity and gastrointestinal toxicity are high. As a broad-spectrum antifungal drug, fluconazole not only has the advantages of stability, good water solubility, high bioavailability and low toxicity, but also is easy to penetrate all eye tissues, especially in the cornea. Therefore, fluconazole is the most widely used antifungal drug in China, but its therapeutic effect is limited because of its high resistance to some Aspergillus and Fusarium [4]. Voriconazole is the second generation of triazole antifungal agents newly developed in recent years, and it is a derivative of fluconazole. It not only has good penetration in the eye, but also has better antifungal efficacy and antifungal spectrum than fluconazole. In particular, the therapeutic effect on Fusarium is better than that of fluconazole and amphotericin B [5].

3. New Nanometer Preparation

3.1. Nanometer Micelle

Micelles are often used as the first choice for the treatment of ocular inflammation, and have been used in anti-fungal keratitis, including polymer micelles and surfactant micelles. Polymer micelle is a kind of shell-core polymer. The shell keeps the micelle stable and the core can effectively improve the availability of drugs. it is found that polymer micelle can not only improve the corneal permeability of antifungal drugs but also prolong the retention time on the corneal surface. improve the effect of drug treatment. Surfactant micelles can increase intracellular permeability by changing the physical properties of corneal epithelial lipid bilayers, down-regulating the expression of P-glycoprotein, and enhancing drug uptake by endocytosis to effectively enhance drug solubility and corneal permeability. it is often used in eye targeted therapy of drugs [6].

3.2. Nano-Hydrogel and Nano-Suspension

Nano-hydrogel is a kind of delivery system in which nanoparticles are dispersed in thermosensitive gel or hydrogel. Thermosensitive gel is a kind of temperature-sensitive hydrogel, which exists in liquid form at low temperature, but forms rapidly at 37˚C. It was found that compared with ordinary eye drops, eye thermosensitive gel could significantly prolong the retention time of the drug in the cornea and improve the bioavailability of the drug [7]. Nano-suspension uses surfactant as suspending agent to disperse drug particles in water to form stable nano-colloidal dispersion. It is a drug-loading system suitable for low water-soluble drug delivery in the eye, which can effectively increase drug solubility and prolong drug surface residence time, but compared with other nano-drug-loading systems, nano-suspension has simpler preparation process and larger drug loading [8]. However, its stability is insufficient, the storage time is short under the same conditions, and there may be irritation and toxicity to the eyes [9], so its further application in clinic remains to be studied.

3.3. Lipid Nanoparticles

Lipid nanoparticles mainly include solid lipid nanoparticles and nanostructured lipid carriers. Solid lipid nanoparticles, which are composed of solid lipids dispersed in 100 - 150 nm surfactant aqueous solution, are a classical substitute for colloidal carrier system. They have lipophilicity, small particle size, can effectively penetrate various physiological barriers, and have the advantages of strong drug loading capacity, high penetration, stability, low physiological toxicity and so on [10]. Nanostructured lipid carrier is an efficient ophthalmic drug delivery system, which can make the drug release continuously without harming the vision. Nanostructured lipid carrier is a kind of liquid dispersion with low viscosity, which is composed of solid lipid matrix and a certain content of liquid lipid. Compared with solid lipid nanoparticles, solid lipid nanoparticles have more advantages, such as delaying drug release, effectively reducing drug leakage during storage, and having stronger ability to load hydrophobic drugs [11]. Although the two kinds of lipid nanoparticles have strong carrying capacity for fat-soluble substances, the carrying capacity for water-soluble substances is insufficient. It limits the clinical application of water-soluble antifungal drugs such as captophenjing and micafungin.

4. New Antifungal Preparation

1) The representative antifungal drug of echinococcins is micafungin, which kills fungi by inhibiting the synthesis of β-1maginan, which is unique to fungal cell wall, and has strong killing effect on Candida and Aspergillus, but it has weak effect on Fusarium. Through the comparative study of the efficacy of micafunjing eye drops and fluconazole eye drops in animal models, some clinical researchers found that the ocular surface and anterior chamber reaction caused by micafungin eye drops was lighter than that of fluconazole, and the ability to reduce fungal hyphae was stronger. However, some researchers selected some patients for clinical randomized controlled trials and found that there was no difference between micafungin and fluconazole in treatment cycle, efficacy and recurrence rate of infection [12]. Therefore, more clinical studies are needed to collect evidence for the clinical application of micafungin.

2) Acrylamines are another antifungal drug developed in recent years, which is represented by terbinafine, which specifically hinders the synthesis of ergosterol in fungal cell membrane by inhibiting squalene cyclooxygenase. Aspergillus and Fusarium are common pathogens of fungal keratitis. However, terbinafine eye drops affect the PH and osmotic pressure of the ocular surface environment, when deviating from the normal ocular physiological PH and osmotic pressure; it will cause a larger ocular surface irritation response [13]. Therefore, the wide use of terbinafine in the treatment of fungal keratitis remains to be considered.

3) Some studies have found that there are antimicrobial peptides in ocular surface tissue, and antimicrobial peptides and their derivatives have excellent antifungal activity, biosafety and corneal permeability. These substances are of

great significance for sterilization and anti-inflammation and maintaining the homeostasis of ocular surface microenvironment [14], but the amount of antimicrobial peptides produced by human eye surface is too small to remove pathogens, and natural antimicrobial peptides are a natural host defense protein. Although it has broad-spectrum antibacterial activity, it is difficult to extract and develop because of its problems such as immune tolerance, high extraction cost and poor protease stability. Therefore, many studies are devoted to the artificial synthesis of antimicrobial peptides by simulating natural antimicrobial peptides. Improve the antibacterial properties, safety and biocompatibility of antimicrobial peptides while improving the defects of natural antimicrobial peptides. Therefore, synthetic antimicrobial peptides are of great clinical significance and application prospect in the treatment of fungal keratitis.

5. Immunosuppressant

The virulence of fungi and the decrease of host immunity are important factors affecting the development of infection. After corneal epithelial damage, fungal spores adhere and destroy the basement membrane. Most pathogenic fungi rely on toxins or hydrolases to invade the corneal stroma, while Fusarium directly destroys the basement membrane and penetrates into the stroma. The increase of inflammatory cells in the stroma and the release of metalloproteinases aggravate the tissue damage. Some experiments in vitro found that after Aspergillus fumigatus was added to the cultured human corneal epithelial cell line, TLR2 and nucleotide binding oligomerization domain-2 were significantly up-regulated, and stimulated the increase of inflammatory factors such as IL-6, IL-8, TNF-α. Therefore, it is suggested that the application of inflammatory factor inhibitors or immunomodulators may be an effective way to treat fungal keratitis [15].

Rapamycin, a macrolide antibiotic, is a low toxic antifungal drug. Because of its immunosuppressive effect, rapamycin has been widely used in the treatment of organ transplantation and other fields. Some studies have found that rapamycin can inhibit the expression of monocyte chemokine-1 and avoid immune injury. Therefore, rapamycin can inhibit the reproduction and infiltration of fungi in the early stage of fungal keratitis infection, reduce the direct damage of fungal hyphae to the cornea, and reduce the excessive immune response of the body, thus it is a good treatment of fungal keratitis. Nearly 71% of patients with fungal keratitis, even through active clinical treatment, will still leave corneal scars due to autophagy system disorders, resulting in a serious decline in the quality of life of patients. It has been found that rapamycin can down-regulate corneal scarring related factors α-smooth muscle actin and transforming growth factor-β by inducing autophagy, improve the survival rate of corneal epithelial cells and alleviate corneal inflammation. Reduce the degree of corneal scarring [16]. Therefore, rapamycin has multiple effects such as anti-immune rejection, inhibition of inflammation, induction of autophagy and anti-scar, indicating that rapamycin has great potential in the treatment of fungal keratitis.

6. Glucocorticoid

Many clinical studies have confirmed that glucocorticoid can thicken fungal hyphae and thicken fungal cell walls, prevent neutrophils from destroying mycelium, increase the adhesion of fungal spores to host and antifungal drug resistance, enhance fungal fecundity and invasiveness, reduce local immunity of corneal tissue and enhance susceptibility to fungi. It aggravates the condition of fungal keratitis [15] and is therefore prohibited in the routine treatment of fungal keratitis. However, in a retrospective study conducted from 2000 to 2006, the clinical characteristics and therapeutic effects of corticosteroids and non-glucocorticoids in the initial treatment of fungal corneal ulcers were compared. The results showed that the operation rate and treatment failure rate were higher in the glucocorticoid group, and deep corneal infiltration was the main factor for treatment failure [17]. One week after keratoplasty, local glucocorticoid eye drops can quickly control anterior segment inflammation, reduce immune rejection, and do not lead to fungal recurrence [18]. Therefore, glucocorticoid should be used cautiously and reasonably in the clinical treatment of fungal keratitis.

To sum up, with the continuous progress of medical level in our country and the unremitting efforts of clinical researchers, great progress has been made in the clinical treatment of fungal keratitis on the basis of previous treatment, especially the emergence of new antifungal drugs with a wider spectrum, which provides more possibilities for improving the vision of patients with fungal keratitis in China. Although the toxicity of some drugs can not be reduced to the least, and some drugs still lack enough clinical research and confirmation, it is believed that with the continuous improvement and progress of clinical practice and clinical research of ophthalmologists, for the treatment of fungal keratitis, drugs with lower toxicity, more affordable, and better efficacy will come to the future pharmaceutical market.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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