



A Review of Antimicrobial Therapy for Infectious Uveitis of the Posterior Segment

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ABSTRACT

Treatment of infectious posterior uveitis represents a therapeutic challenge for ophthalmologists. The eye is a privileged site, maintained by blood ocular barriers, which limits penetration of systemic antimicrobials into the posterior segment. In addition, topical and subconjunctival therapies are incapable of producing sufficient drug concentrations, intraocularly. Posterior infectious uveitis can be caused by bacteria, virus, fungi, or protozoa. Mode of treatment varies greatly based on the infectious etiology. Certain drugs have advantages over others in the treatment of infectious uveitis. Topical and systemic therapies are often employed in the treatment of ocular infection, yet the route of treatment can have limitations based on penetration, concentration, and duration. The introduction of intravitreal antimicrobial therapy has advanced the management of intraocular infections. Being able to bypass blood-ocular barriers allows high drug concentrations to be delivered directly to the posterior segment with minimal systemic absorption. However, because the difference between the therapeutic and the toxic doses of some antimicrobial drugs falls within a narrow concentration range, intravitreal therapy could be associated with ocular toxicity risks. In many cases of infectious uveitis, combination of intravitreal and systemic therapies are necessary. In this comprehensive review, the authors aimed at reviewing clinically relevant data regarding intraocular and systemic antimicrobial therapy for posterior segment infectious uveitis. The review also discussed the evolving trends in intraocular treatment, and elaborated on antibiotic pharmacokinetics and pharmacodynamics, efficacy, and adverse effects.

KEYWORDS

Endophthalmitis; Infectious Uveitis; Intraocular Infection; Intravitreal; Intracameral; Antimicrobials; Antifungal; Antiviral; Antibacterial; Retinitis; Toxoplasma

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INTRODUCTION

Infectious posterior uveitis is an uncommon type of uveitis. It can occur after ocular surgery or trauma, as a consequence of systemic infection, or due to activation of latent infection. Because posterior segment infectious uveitis is a sight threatening disease, early recognition with prompt treatment is fundamental to prevent severe loss of vision [1]. The success of treating infections with antimicrobial therapy depends on the characteristics of the particular pathogen, e.g. the virulence of the organisms and the rate of regrowth of persistent organisms, as well as host- and drug-related factors, including the initial load, pharmacokinetic and dynamic characteristics of the antimicrobial agent, and the host immune mechanisms [2].

Despite advances in diagnostic techniques and the introduction of new antimicrobial drugs, treatment of infectious uveitis remains a therapeutic challenge. The eye is a privileged site, maintained by blood ocular barriers, which limits penetration of systemic medications to the posterior segment. Over the past two decades, intravitreal drugs have revolutionized the outcomes of vitreoretinal diseases, including uveitis. Advantages of intravitreal therapy in infectious uveitis include circumvention of blood-ocular barriers with direct delivery of antimicrobial drugs as well as decreased systemic drug absorption [3].

Blood-ocular Barriers

The blood ocular barrier separates the ocular tissue from blood circulation, responsible for active and passive exchange between circulation and intraocular structures. It is divided to the blood-retinal barrier and the blood-aqueous barrier. In a normal physiologic state, the eye is poorly penetrated by systemic drugs; and thereby, achievement of high intraocular concentration is hindered. However, blood ocular barriers can be penetrated with ideal tissue pH, molecular weight, lipophilicity, and ionization with variable degree [4]. The blood-aqueous barrier is located at the endothelium of the iris vessels and the non-pigmented ciliary body epithelium, in which tight junctions form the main sites of resistance for drug diffusion to the aqueous humor. The pigmented epithelium and non-pigmented epithelium of the ciliary body are divided by tight junctions, composed of proteins, such as claudin-1, occludin, and ZO-1 [5, 6]. The blood-ocular barrier can be broken down or bypassed in certain non-physiological states, including intraocular inflammation and following surgical procedures [7].

The blood-retinal barrier is further divided to the outer and inner blood retinal barrier. The outer blood-retinal

barrier, composed of tight junctions and adjacent adherens junctions, separates the sub-retinal space from the choroidal circulation. The inner blood-retinal barrier is analogous to the blood-brain barrier and formed by tight junctions of the endothelial cells of retinal blood vessels [4, 8]. The blood-retinal barrier is compromised by a variety of insults, such as chemical, thermal, or traumatic injury to the retinal vessels. The degree of leakage can be quantified using vitreous fluorometry and more accurately mapped by the Retinal Leakage Analyzer, a modified confocal laser ophthalmoscope scanning technique [9]. In contrast to the retinal vasculature, the blood supply to the choroid is enormous with large fenestrations of 20 to 40 micrometer (μm) in the choriocapillaris, allowing diffusion of molecules at high concentration to the choroidal tissue and the sub-retinal space [10].

To obtain therapeutic drug concentrations in the vitreous and the retina requires either systemic or intravitreal drug administration as opposed to subconjunctival or sub-Tenon route, which are unable to reach sufficient concentrations. High doses of systemic medications are needed to achieve adequate concentrations in the vitreous, due to limited blood flow and the blood-retinal barriers. Moreover, systemic absorption of drugs may lead to undesirable adverse events. However, because of the anatomical characteristics of the choroidal circulation, systemic medications reach the choroid at high concentrations, thus, infections, mainly confined to the choroid/outer retina, such as TB choroiditis and early fungal chorioretinitis, can be adequately managed with systemic antimicrobials alone [10].

Compared to the systemic route, intraocular injections of antimicrobial drugs to the vitreous cavity allows rapid delivery of very high drug concentrations to the posterior segment, as it bypasses blood-retinal barriers. This is of significant benefit in patients, who have sight threatening infections involving zone 1 (defined as 3000 μm from the fovea or 1500 μm from the optic nerve head) of the retina [11]. As the concentrations of antimicrobial drugs in the vitreous, achieved after intravitreal injection, significantly exceeds the Minimum Inhibitory Concentration (MIC) for common organisms (Super-MIC), the majority of antibiotics are likely to be bactericidal at these concentrations. Because bacterial kill rate is a function of drug concentration and contact time, it is possible that intravitreal antibiotics may also have an effect for longer than expected, even as their concentration decreases. Additionally, bacteria may create biofilms around intraocular lens implants that



make them less susceptible to antibiotics [12]. Very high drug concentration is needed to inhibit bacterial growth within these biofilms, and this could only be achieved via intravitreal drug administration.

Intraocular therapy also offers the opportunity to avoid adverse effects of systemic medications, which is of particular significance in pregnant or systemically ill patients. However, intraocular drug administration has several caveats. Since the adequate therapeutic level of most drugs usually falls in a narrow concentration range, decreasing ocular toxicity requires explicit control of drug concentration and injection volume. Also, intravitreal treatment does not provide treatment for the fellow eye or for any associated systemic infection, thus, it may not be sufficient alone in certain types of infectious uveitis. Other drawbacks include a small risk of injury to the crystalline lens or retina during the injection, as well as the risk of endophthalmitis [13].

Pharmacokinetics of Intraocular Therapy

Various models have been designed to study the pharmacokinetics of intravitreal injection [14, 15]. Tojo and Isowaki designed a model, which assumed a cylindrical vitreous body in contact with a retinal/choroidal/scleral membrane on one side and the posterior capsule and aqueous humour on the other. This model suggested that drug molecules first diffuse through the vitreous and then move to surrounding tissues. The drug molecules are mainly released from the vitreous, through the aqueous humour. Secondly, drug elimination takes place posteriorly by active and passive transport across the blood-retinal barrier. In general, drugs that are eliminated through the aqueous humour route, have longer half-life than those cleared from the vitreous via the posterior route [16]. Large molecules and cationic drugs (e.g. aminoglycosides and vancomycin) are primarily cleared through the anterior route while small molecules and anionic drugs (e.g. cephalosporins and clindamycin) are eliminated via the posterior route. In addition to the physical properties of drugs, ocular inflammation and previous ocular surgery (i.e. cataract removal, vitrectomy) can also influence the half-life of drugs in the vitreous. In inflammation, active transport through the blood-retinal barrier is decreased, causing decreased elimination of drug [17], while elimination through the anterior route through the aqueous is increased [18]. In aphakia, clearance of drugs that are mainly eliminated through the aqueous are enhanced, while vitrectomy surgery results in rapid clearance of antimicrobial drugs that depend on the posterior route [19, 20]. Notably, however, the use of vitreous tamponade in vitrectomised eyes may delay the

elimination of intravitreal antibiotics from the vitreous cavity, and reduction of intravitreal antibiotics doses in silicone-filled eyes has been recommended to decrease the risk of retinal toxicity [21].

Pharmacodynamics of Antimicrobial Drugs

Antibiotics are divided to two main classes, according to their antibacterial activity, and bacteriostatic and bactericidal properties. Bacteriostatic drugs (e.g. clindamycin, and trimethoprim/sulfamethoxazole) function by inhibiting the growth or replication of bacteria. This, however, does not result in bacterial death, and, therefore, elimination of the bacteria requires assistance from the host immune system. In contrast, bactericidal drugs (e.g. cephalosporins, vancomycin, gentamycin, amikacin, and moxifloxacin) induce bacterial killing. A clear distinction between these two classes is not always possible, for instance, bacteriostatic drugs may induce bacterial killing, if used at high concentrations [2].

The minimum inhibitory concentration (MIC) of an antibacterial agent is defined as the lowest concentration, at which it suppresses the growth of 10^5 colony forming units of bacteria/mL, after adequate incubation [22]. Minimum bactericidal concentration (MBC) is considered as the gold standard for evaluating susceptibility of microorganisms to antimicrobial agents and is used to determine the potency of antimicrobial agents. The minimum drug concentration, which decreases $\geq 99.9\%$ of the viability of the bacteria, is known as MBC. For bactericidal drugs, the MBC is usually not more than four folds greater than the MIC, and drug concentrations of proven clinical efficacy are about 10 folds higher than the MIC for most bacteria [2].

Bactericidal drugs can be further subdivided, according to their killing mechanism to two groups. First are concentration-dependent bactericidal drugs (e.g. aminoglycosides), in which the rate and extent of bacterial killing are directly related to the concentration of the drug. Thus, the dosing strategy should aim at achieving levels that are much higher than MBC. The second group is the time-dependent bactericidal drugs (e.g. vancomycin and cephalosporins), where efficacy is mainly dependent on the time, at which exposure is maintained above the MBC and, thus, progressive escalation of drug concentrations would not further enhance the bactericidal activity [23].

Use of the Suprachoroidal Space

Utilization of the Suprachoroidal Space (SCS) has been a topic of recent interest in its ability to locally treat intraocular disease [24]. Suprachoroidal injection has been postulated as a potential treatment for posterior



uveitis, macular edema, glaucoma, Age-related Macular Degeneration (AMD), stem cell therapy, and retinal prostheses [24]. Access to the SCS has been accomplished by cannulation and hypodermic needle, yet recent microneedle delivery at the limbus is of particular interest due to easier access and enhanced safety. In an experiment accessing the SCS of mouse eyes, molecules and particles were shown to have targeted the chorioretinal region from seconds to months, depending on the size of the substances. Eluting drugs could possibly be used due to the sieve-like elimination of drug particles [24]. Molecular clearance from the SCS tends to be eliminated via three pathways. Within 10 minutes, fluid and molecules exit by diffusion into the sclera and choroid, and pressure-driven movement through transscleral leakage sites. Within one hour, molecules exit through the choroidal vasculature. Finally, between one and ten hours, molecules exit through the scleral, secondary to diffusion and convection [24]. Chen et al. [25] showed that in mice eyes, aqueous humor, peak concentrations in the posterior portion of the vitreous, and retina were 0.69 nanogram/milliliter (ng/mL), 1 912 ng/mL and 400 369 ng/mL, respectively, after 50 microliter (μL) of triamcinolone acetate suprachoroidal injection. Ocular distribution studies in rabbits showed a 10-fold higher concentration of triamcinolone in the posterior segment after SCS injection when compared to intravitreal injection, and a 10-fold increase in chorioretinal selectivity after six hours, defined as concentration in the chorioretinal tissues compared to concentration in the lens [26]. Although accessing the SCS does not involve complete penetration of the globe, complications include suprachoroidal hemorrhage and increased intraocular pressure [24].

Antibacterial Therapy

Rationale for Treatment

Bacterial endophthalmitis may occur after intraocular surgical procedures (postoperative), following penetrating trauma (post-traumatic) or as a result of haematological spread from a distant site of infection (endogenous). The majority of cases of bacterial endophthalmitis are encountered after cataract surgery and intravitreal injections.

While intravitreal therapy is the main stay for posttraumatic and postoperative infection, the rationale of treatment in endogenous endophthalmitis is based on treatment with both systemic antibiotics to treat the source of infection, as well as intravitreal therapy, to treat the intraocular infection [27]. Choice of systemic antibiotic is mainly guided by the nature of systemic infection with preference given to medications that have

good penetration in the posterior segment. There is data to suggest that quinolones, particularly moxifloxacin, that have better intraocular penetration, may have a beneficial impact on visual outcome [28, 29]. The role of Pars Plana Vitrectomy (PPV) in endogenous endophthalmitis is not clearly defined yet there appears to be a trend towards early PPV. Early vitrectomy in endogenous endophthalmitis secondary to *Klebsiella pneumoniae* was shown to improve visual acuity to HM or better, in 50% of eyes, while preserving all eyes anatomically in the study [30]. A randomized study of 108 eyes with endogenous endophthalmitis showed that eyes with vitrectomy plus Silicone Oil (SO) tamponade were more likely to have successful outcomes, defined as vision of counting fingers at one meter or better and less risk of retinal detachment: Eyes with SO tamponade achieved success in 63.7% of cases compared to 43.4% in eyes solely with PPV [31].

Intravitreal Vancomycin

Mechanism of Action and Pharmacokinetics

Vancomycin is a bactericidal agent that causes cell lysis through prevention of the polymerization of peptidoglycan in the cell. Ferencz et al. reported that therapeutic vitreous vancomycin concentrations were only achieved with intravitreal treatment and not intravenous administration for the treatment of gram-positive endophthalmitis [32]. Though some physicians use a dose of two milligrams (mg), the commonly used intravitreal dose of vancomycin is 1 mg, as recommended by the endophthalmitis Vitrectomy Study (EVS) [33]. This dosage results in vitreous concentration that is significantly higher (50 to 200-fold) than MIC of most gram positive organisms. Vancomycin has a half-life in the vitreous, from 25 to 56 hours, as demonstrated in infected rabbit eyes, with drug concentration being maintained above bactericidal level for up to 72 hours [34, 35]. As the antibacterial activity of vancomycin is mainly time-dependent rather than concentration-dependent, some authors recommend an alternative smaller dose regimen of 0.2 mg with repeat injection using the same dose after three to four days [36].

Spectrum of Activity And Resistance

Vancomycin has been the antibiotic of choice for coverage of gram-positive organisms, given the increased incidence of β -lactam antibiotic resistance. Vancomycin achieves nearly 100% efficacy for the treatment of gram-positive endophthalmitis (including methicillin-resistant *Staphylococcus* species), yet it does not have any significant activity against gram-negative organisms [37].



Vancomycin resistance is rare, however, it is seen in some cases with *Bacillus* and *Enterococcus* species [38].

Adverse Effects

Vancomycin is reported to be safe in doses up to 2 mg in rabbit eyes [39]. Mochizuki et al. found that a dose of 1.0 mg of vancomycin caused no electroretinographic changes for at least eight weeks after injection in rabbit eyes. However, with a higher dose of 10 mg, the Electroretinogram (ERG) was non-recordable with only partial recovery afterwards [40]. Intracameral vancomycin is controversial, given its historical association with postoperative macular edema. Axer-Siegel et al. reported, in a randomized controlled trial, a 2.8-fold risk of cystoid macular edema after using intracameral vancomycin during extracapsular cataract extraction, as prophylaxis against postoperative endophthalmitis [5]. However, more recent Optical Coherence Tomography (OCT)-based studies showed no difference in retinal thickness after intracameral vancomycin as compared to either no antibiotics or to intracameral cefuroxime [41]. Witkin et al. reported Hemorrhagic Occlusive Retinal Vasculitis (HORV) in 36 eyes of 23 patients receiving intraocular vancomycin. Thirty-three of 36 eyes received intracameral bolus following cataract extraction, while one received intravitreal injection and two received vancomycin via an irrigation bottle. Visual prognoses were poor in the majority of cases. The authors suggest a type III hypersensitivity reaction, based on timing and clinical presentation of symptoms [42] [43]. Further insight in the pathophysiology of HORV, based on histologic specimen, revealed a predominately T-cell, non-granulomatous inflammatory component, confined completely to the choroid, without evidence of leukocytoclastic vasculitis as had been previously theorized. Ultrasound biomicroscopy revealed severely ischemic iris and ciliary body, which was corroborated on the histologic specimen [44].

Intravitreal Ceftazidime

Mechanism of Action and Pharmacokinetics

Ceftazidime is a third-generation cephalosporin, which broadly covers gram-negative bacteria, including *Pseudomonas aeruginosa*. Ceftazidime is bactericidal and lyses bacteria by cross-linking of the cell wall via a transpeptidase reaction. The half-life of ceftazidime in phakic rabbit eyes is 13.8 hours [45]. When combined with vancomycin, ceftazidime forms a precipitate in solution, likely secondary to the alkalinity of vancomycin and the acidity of ceftazidime. Therefore, it is recommended to inject the two antibiotics, separately.

Alternatively, a small air bubble can be aspirated in between the two medications, if one prefers fewer injections in the eye.

Spectrum of Activity and Resistance

Ceftazidime has a broad therapeutic index and high in-vitro antimicrobial activity, administered at a dose of 2.25 mg/0.1 mL [46, 47]. Irvine et al. found that gram-negative endophthalmitis isolates had sensitivities of 100% to ceftazidime and 97% to amikacin [48]. A review corroborated these results, showing higher sensitivities to ceftazidime compared to aminoglycoside in isolates with gram-negative endophthalmitis [49]. It is possible that bacterial resistance to ceftazidime could vary from one geographical region to another, as several studies originating from India reported high rates of resistance in gram-negative organisms, ranging from 18% to 49% [50, 51].

Adverse Effects

Use of intravitreal ceftazidime appears safe and has not been associated with signs of retinal toxicity for doses up to 10mg/0.1 mL in primates [52].

Intravitreal Amikacin and Gentamicin

Mechanism of Action and Pharmacokinetics

The aminoglycosides, gentamicin, and amikacin, are bacteriostatic and disrupt cell replication by binding to the 16S ribosomal RNA within the 30S ribosomal subunit, and halts genetic production. This subsequently leads to the interruption of bacterial protein synthesis [53].

Spectrum of Activity and Resistance

Aminoglycosides protect mainly against gram-negative bacteria and may also have some advantages over other gram-negative antibiotics (e.g. ceftazidime). Aminoglycosides are not dependent on the inoculum size and can exhibit synergy with vancomycin against gram positive cocci. However, data from clinical studies showed no significant differences in visual outcomes, in treatment with ceftazidime versus amikacin, including eyes with bacterial endophthalmitis [53]. There are increasing numbers of resistant bacterial strains to aminoglycosides, such as those forming aminoglycoside-modifying enzymes that result in poor drug binding to ribosomes [54]. Intravitreal amikacin, which is more commonly used than gentamicin, is dosed at 0.4 mg/0.1 mL and has a vitreous half-life of 25.5 hours in phakic, uninfamed rabbit eyes [20].

Adverse Effects

Aminoglycoside toxicity is well-documented in the literature. Retina and retinal pigmented epithelium are damaged at doses close to therapeutic levels, which is



thought to be, in part, due to retinal ischemia [55]. Some drugs in the aminoglycoside family seem to have a more profound toxicity on ocular tissues. Gentamicin has been found to have greater retinal toxicity than amikacin in rabbit eyes [56, 57]. Notably, aminoglycoside-induced retinal infarction is uncommon with one out of 420 eyes reported in the EVS, after treatment with intravitreal amikacin [33].

Intravitreal Moxifloxacin

Mechanism of Action and Pharmacokinetics

Moxifloxacin interacts with topoisomerase II (DNA gyrase) and topoisomerase IV to interfere with bacterial DNA synthesis [58].

Spectrum of Activity and Resistance

The spectrum of quinolones has advantageous activity against gram-positive and gram-negative bacteria. Fourth generation quinolones, such as moxifloxacin and levofloxacin, have extended gram-positive activity, in comparison to earlier generations of quinolones. However, ciprofloxacin, a second generation quinolone, has better coverage against pseudomonas species [4, 59-61]. When compared to vancomycin, the efficacy of intravitreal moxifloxacin has demonstrated similar histopathological, bacteriological, and clinical outcomes in animal studies comparing treatment of *Staphylococcus aureus* endophthalmitis [62]. Resistance to this drug is, however, increasing; the most commonly noted are methicillin-sensitive *Staphylococcus epidermidis* isolates [63]. A study examining 327 isolated gram-positive organisms in patients with endophthalmitis found isolate sensitivities of 47% to moxifloxacin versus 100% to vancomycin [64]. The current recommended dose is 500 µg/0.1 mL in order to achieve a vitreous concentration of approximately 125 µg/0.1 mL [65]. Along with increasing resistance, the limited vitreous half-life of moxifloxacin is also of concern. Lyer et al. showed that intravitreal moxifloxacin has a 1.72-hour half-life, and is only eliminated from the vitreous through both aqueous and posterior route. Nevertheless, vitreous concentrations surpassed the MIC of 90% of common endophthalmitis-causing organisms (MIC₉₀) by one to several orders of magnitude, after 12 hours, when investigated in uninfamed phakic rabbit eyes [66].

Adverse Effects

Though clinical studies are limited, intravitreal use of moxifloxacin is considered safe [62, 67]. In addition, electrophysiological studies performed on rabbit eyes and as part of in vitro studies of human RPE cells demonstrated that concentrations of up to 150 µg/mL do not cause retinal damage [68, 69]. However, adverse

effects have been observed with intracameral use of moxifloxacin, following ocular surgery. A recent meta-analysis showed increased central corneal thickness and macular thickening as possible side adverse effects, although, many of the studies found no significant changes in the cornea or macula following intracameral use of moxifloxacin [70].

In summary, empirical broad spectrum intravitreal antibiotics remains the standard treatment for bacterial endophthalmitis. Intravitreal vancomycin is the consensus intravitreal anti-infective choice to treat gram-positive endophthalmitis, despite some evidence of emerging vancomycin-resistant bacteria in 11% of culture-proven isolates [71]. While in the EVS, [33] intravitreal vancomycin and amikacin was injected in all eyes, contemporary data indicates increased preference for the use of a third-generation cephalosporin, in particular ceftazidime over amikacin for gram-negative coverage because of concerns of aminoglycoside-related toxicity [72] [73].

Antifungal Therapy

Rationale for Treatment

Fungal endophthalmitis is commonly encountered as a complication of systemic fungal infection, yet can also occur following intraocular surgery or penetrating trauma [74-76]. The most common fungal pathogens, include *Aspergillus spp.* and *Candida spp.* Emergence of *Fusarium spp.* and *Scedosporium spp.* has been reported more recently. Intraocular fungal infection is primarily a foci of hematogenous spread from systemic infection; therefore, systemic antifungal therapy is usually required with a preference for fluconazole and voriconazole, given their ability to achieve high drug concentration in the vitreous and ocular tissues [74-76]. In general, flat lesions involving the choroid/outer retina can only be managed with systemic treatment because of the rich blood supply of the choroid, while lesions extending to the inner retina and the vitreous are usually treated with a combination of systemic antifungal therapy and intravitreal injections [74-76]. Vitrectomy is a commonly used modality in treatment of fungal endophthalmitis. However, the role and the ideal timing of vitrectomy in a course of fungal endophthalmitis is unclear. According to a retrospective study of 44 eyes with endogenous *Candida* endophthalmitis by Sallam et al., early PPV, within one week of presentation, did not significantly reduce the risk of profound visual loss (postoperative Snellen acuity of ≤20/200), yet it decreased the risk of retinal detachment by five folds [74]. A recent large retrospective cohort showed immediate vitrectomy, performed at the time of initial injection of antimicrobial agents, to be associated



with significant visual acuity improvement (mean logarithm of the minimum angle of resolution (logMAR) 2.534 to 2.153, $p=0.027$) in eyes with culture-proven fungal endophthalmitis as compared to no significant visual acuity improvement (mean logMAR 2.336 to 2.367, $P = 0.844$) in eyes, where vitrectomy was deferred. However, there was no difference in the absolute postoperative visual acuity or the proportions of eyes reaching a postoperative acuity of 20/200 [77].

Amphotericin B

Mechanism of Action and Pharmacokinetics

Although the use of intravitreal fluconazole in human eyes has previously been described, until recently, Amphotericin B (AMB), a polyene antifungal, was the main intravitreal antifungal drug, routinely used in clinical settings [24]. Amphotericin B utilizes ergosterol on the cell membrane to form complex creating pores within the membrane and causes cell death. Amphotericin B has a relatively long half-life in the vitreous after intravitreal administration, ranging from 6.9 to 15.1 days. The recommended intravitreal dose of AMB is in the range of 5 to 10 μg . There is no standardization of the number or time of repeat injections due to a variety of factors, aside from a four-fold increase in elimination after vitrectomy. Subsequent injections depend on the clinical response of the eye after initial injection, amount of retinal-ocular compromise from inflammation, and states of the vitreous cavity [78].

Spectrum of Activity and Resistance

Amphotericin B has a wide spectrum of activity against several fungal species [75]. However, recent reports have revealed increased resistance of a few non-*Candida albicans* species [79]. Moreover, AMB resistance has been clinically observed with other fungi, such as *Aspergillus spp.* and *Fusarium spp.* [75].

Adverse Effects

Reports have shown the risk of development of focal toxicity of the retina with doses as low as 1 μg [4]. Increased rates of vitreous inflammation and extensive retinal necrosis were also reported with higher intravitreal concentrations [80, 81].

Voriconazole

Mechanism of Action and Pharmacokinetics

Voriconazole, a second-generation triazole, is a newer drug, reserved for the treatment of severe fungal infections. Similar to other triazoles, voriconazole inhibits 14- α -demethylase, a cytochrome p-450 enzyme, thereby, interfering with ergosterol synthesis, which results in

lysis of the fungal cells. Voriconazole showed good ocular bioavailability when used systemically (oral or intravenous), achieving therapeutic levels in both the vitreous and the aqueous humor [82]. Pharmacokinetic studies of intravitreal voriconazole demonstrated that drug levels achieved during the first eight hours are at least 10 folds greater than the MIC of most fungal organisms, causing endophthalmitis. However, because its half-life in the vitreous is as short as 2.5 hours and drug concentration exhibits early exponential decay, repeat intravitreal treatment to maintain a therapeutic level is usually required [83].

Spectrum of Activity and Resistance

Voriconazole has an extremely effective spectrum of activity against yeasts and molds. It was shown to be efficacious when used for *Aspergillus spp.*, *Blastomyces dermatitidis*, *Candida spp.*, *Coccidioides immitis*, *Cryptococcus neoformans*, and *Histoplasma capsulatum* [84]. A recent retrospective study of 47 fungal isolates from yeast and mold infection in eyes with fungal endophthalmitis, reported 100% susceptibility of the isolates to intravitreal voriconazole, as compared to only 69% to intravitreal AMB [75].

Adverse Effects

Intravitreal voriconazole has been shown to be associated with a lower risk of retinal toxicity when compared to animal models utilizing intravitreal AMB. In rat retinas, no histopathological or electroretinographic changes were seen, even with concentrations of up to 25 $\mu\text{g}/\text{mL}$ [85]. Focal areas of necrosis, however, did occur with concentrations of 50 $\mu\text{g}/\text{mL}$ or more. This has led to extrapolation that up to 100 μg of intravitreal voriconazole could be safely used in human eyes. Clinically, such intravitreal voriconazole dosing has not shown evidence of toxicity to the retina [86]. However, the acquisition cost of voriconazole is much higher than that of AMB, which may limit its usefulness in some countries.

Caspofungin

Mechanism of Action and Pharmacokinetics

Caspofungin noncompetitively inhibits $\beta(1,3)$ -D-glucan synthase, which is an enzyme responsible for cell wall formation. Caspofungin has a particularly low oral bioavailability, measuring less than 0.2%, yet, intravenously, has a much higher distribution in most tissues. An exception is in the eye due to its large molecular mass (1,213 Dalton). In vitro, the MIC of caspofungin has been measured at 0.03 to 1 $\mu\text{g}/\text{mL}$ and 0.06 $\mu\text{g}/\text{mL}$ for *Candida* and *Aspergillus spp.*, respectively. In rabbit eyes, mean vitreous concentration was 6.06 ± 1.76 $\mu\text{g}/\text{mL}$ after caspofungin injection, which



was well-above the MIC. However, like voriconazole, concentrations rapidly decreased due to exponential decay, despite having a longer half-life of 6.28 hours [87].

Spectrum of Activity and Resistance

Caspofungin has a narrower spectrum of coverage when compared to voriconazole [84]. However, the MIC for *Candida* and *Aspergillus species* is much higher with voriconazole than caspofungin. A recent case report showed resolution of endophthalmitis in patients with AMB-, fluconazole-, and voriconazole-resistant *Candida ciferrii* [88]. However, in a 15-year review of culture-proven fungal endophthalmitis, isolates showed sensitivities of 70% with caspofungin compared to 93% with voriconazole [89].

Adverse Effects

Caspofungin has an excellent safety profile when injected into the intravitreal space in animal models with one study showing normal ERGs after injection of 10 to 200 μ L of caspofungin into rabbit eyes [87]. Although not readily employed, caspofungin may be a viable option in intravitreal treatment of fungal endophthalmitis due to its favourable safety profile [84].

In summary, intravitreal voriconazole is currently the intravitreal treatment of choice of fungal endophthalmitis particularly if infection with mold species cannot be excluded. Intravitreal AMB remains a reasonable alternative in eyes with fungal endophthalmitis due to yeast when voriconazole use is not feasible.

Antiviral Therapy

Rationale for Treatment

Cytomegalovirus (CMV) is a common cause of infectious retinitis. It is the most common cause in defective T-cell-mediated immunity conditions, such as AIDS, lymphoreticular and malignancies, and in patients on long-term immunosuppressive medications. Retinitis due to CMV has also been reported following intraocular immunosuppressive therapy in immunocompetent patients [90-92].

Current treatment recommendation for CMV retinitis in patients with HIV is mainly dependent on systemic therapy. It has shown to be associated with increased survival and decreased viral dissemination to the fellow eye. Studies performed in the post-Highly Active Antiretroviral Therapy (HAART) also demonstrated superiority of systemic antiviral treatment to repeat intravitreal injections in controlling the retinitis, though in earlier studies, systemic treatment was found to be inferior to sustained release ganciclovir implant in this regard [93]. Intravitreal antiviral therapy is, therefore,

mainly used as an adjunctive treatment for CMV retinitis in patients with HIV, who cannot tolerate or have resistance to systemic therapy. It is also used to supplement systemic therapy in patients with zone 1 disease. There is a paucity of literature on treatment of CMV retinitis in patients without HIV. Recent evidence suggests a possible role for intravitreal antiviral injections not only as an adjunctive to systemic anti-CMV therapy, yet also as an alternative treatment in patients, who are iatrogenically immunosuppressed and in whom cessation of immunosuppressive therapy has resulted in immune recovery. In these non-HIV immunosuppressed patients, 53.84% of eyes had complete resolution of retinal lesions within one month of ganciclovir injections [94].

A separate entity that causes acute necrotizing retinitis is Acute Retinal Necrosis (ARN). Its most common causative etiologies are Herpes Simplex Virus (HSV) or Varicella Zoster Virus (VZV). Few controlled trials have been conducted for the treatment of ARN; therefore, anecdotal evidence primarily guides treatment. Systemic treatment comprised of intravenous acyclovir or oral valacyclovir is the mainstay of treatment for ARN, particularly to provide protection for the fellow eye. Still, intravitreal therapy plays a key role as an adjunctive measure and may decrease the risk of retinal detachment. In one study, Wong et al. showed a reduction in the risk of retinal detachment by 40% (53.6% versus 75.0%) when intravitreal foscarnet was added to systemic treatment in VZV retinitis [95]. Progressive Outer Retinal Necrosis (PORN) syndrome is another form of necrotizing retinitis, caused by VZV that occurs in severely immunocompromised patients and often results in profound loss of vision. Though treatment outcomes in PORN are generally dire, with retinal detachment reported in 51% of eyes and nearly 20% with progression to no light perception, visual results obtained with combination treatment using systemic and local antiviral therapy appears to be superior to systemic therapy alone [96].

Intravitreal Ganciclovir

Mechanism of Action and Pharmacokinetics

Ganciclovir is a guanosine analogue that selectively inhibits DNA polymerase in CMV cells after being activated in vivo by viral and cellular kinases. Data from human eyes treated with intravitreal ganciclovir demonstrated a mean half-life of 18.8 hours after administration with a concentration that remains above the level that is sufficient to inhibit 50% of CMV virus activity (ID_{50}) for up to seven days [97].

Spectrum of Activity and Resistance



Ganciclovir is mainly employed in treating CMV retinitis yet has also been used for treatment of VZV retinitis [96]. An induction dose of 2 mg/0.1 mL of ganciclovir is given intravitreally bi-weekly for two to three weeks, followed by weekly injections for maintenance therapy. Dosages of ganciclovir 3 mg can be given more frequently in combination with intravitreal foscarnet in patients, who cannot tolerate systemic therapy [98, 99].

Adverse Effects

Intravitreal ganciclovir use is generally tolerated without associated decreased visual acuity or ocular toxicity. Even with higher doses of 3 mg, definite signs of retinal toxicity were identified in clinical scenarios; however, histological evidence of mild iris atrophy has been demonstrated [98].

Ganciclovir Implant

Ganciclovir implant releases ganciclovir at a steady state over six months. This device requires surgery to secure it intraocularly to the sclera at the region of the pars plana. The ganciclovir implant has demonstrated superiority over systemic CMV treatment in controlling retinitis progression [93]. Though ganciclovir implant surgery is associated with a low risk of serious postoperative complications, including retinal detachment and ocular hypotony, the risk of vitreous hemorrhage (10%) or endophthalmitis (0.46%) is substantially higher than those observed after intravitreal injections [100, 101]. Since the era of HAART therapy, the incidence of CMV retinitis has decreased in patients with HIV, and the usefulness of ganciclovir implant is limited.

Intravitreal Foscarnet

Mechanism of Action and Pharmacokinetics

Foscarnet is an analog of pyrophosphate, designed to inhibit viral replication through binding to the DNA polymerase enzyme, preventing DNA chain elongation. In contrast to ganciclovir, foscarnet does not require further in vivo activation by viral or cellular enzymes. Lopez-Cortes et al. compared the pharmacokinetics of foscarnet and ganciclovir in a rabbit model. Their results demonstrated that although the half-life of the foscarnet in the vitreous is significantly prolonged (77 hours) than that of ganciclovir (8 hours), drug concentrations found in the retinal tissues were much lower than those for ganciclovir, and decreased more rapidly [102].

Spectrum of Activity and Resistance

Foscarnet inhibits the replication of multiple herpes family viruses and hence could be used for treatment of retinitis due to CMV, HSV and HZV. This makes it particularly useful for treatment of ARN, thereby,

providing good initial control of virus replication until vitreous Polymerase Chain Reaction (PCR) result is received and the specific virus is identified. The induction dosage of intravitreal foscarnet is 2.4 mg/0.1 mL once or twice weekly, followed by once weekly, for maintenance. Though treatment with foscarnet is effective, resistance may sometimes develop [103].

Adverse Effects

Intravitreal foscarnet is tolerated well without report of associated decreased vision or clinical signs of retinal toxicity [98, 99].

Intravitreal Cidofovir

Cidofovir is an antiviral, which inhibits viral DNA synthesis, selectively, thereby, suppressing replication of CMV [104]. Intravitreal cidofovir is a very effective treatment yet is not frequently used due to the exceeding incidence of ocular inflammation, resulting in uveitis and ocular hypotony [105].

Anti-toxoplasma Therapy

Rationale for Treatment

Toxoplasma gondii, an obligate intracellular parasite, is the most common cause of posterior uveitis of infectious origin in immunocompetent individuals [106]. *Toxoplasma*-induced retinochoroiditis is often self-limiting and there is no level I evidence to indicate a substantial benefit of routine antimicrobial treatment in immunocompetent patients. Treatment is usually reserved for active lesions associated with severe vitritis or located in the macula or near the optic nerve [77]. Systemic therapy is the current treatment of choice for ocular histoplasmosis. The aim of drug therapy in treating toxoplasmosis is to decrease the parasitic load without increasing the amount of ocular inflammation. The best treatment medication or regimen is yet to be established, and there are currently more than 20 regimens with at least nine medications commonly used, including sulfadiazine, pyrimethamine as well as clindamycin or trimethoprim/sulfamethoxazole [107]. Because of the potentially serious systemic adverse effects that could be associated with anti-toxoplasma medications and the fact that toxoplasma reactivation is commonly unilateral in immunocompetent patients, there has been recent interest in treating toxoplasma retinitis, solely by intravitreal therapy, instead of systemic medications [108-110].

Intravitreal Clindamycin

Clindamycin is an antibacterial that interferes with protein synthesis by binding to the 50s ribosomal subunit in bacterial cells. In both human and animal eyes, ocular



toxoplasmosis has been successfully treated with clindamycin. Clindamycin has also demonstrated some effects against cystic toxoplasmosis, decreasing the tissue load of the toxoplasma cysts [108].

In two single-masked, clinical trials that comprised of 134 patients with active ocular toxoplasmosis randomized to treatment with either intravitreal clindamycin plus dexamethasone or to systemic therapy with pyrimethamine, sulfadiazine, folic acid and prednisolone, intravitreal clindamycin exhibited benefits in the treatment of *Toxoplasma retinochoroiditis* [108, 111]. After six weeks, no difference was noted in visual acuity, vitreous inflammatory response or lesion size reduction. The rate of retinitis recurrence in two years was comparable between eyes treated with systemic and intravitreal therapy. Major complications secondary to intravitreal injection were not encountered aside from adverse drug reactions in three patients in the systemic treatment arm. In eyes treated with intravitreal therapy, the mean number of injections was approximately 1.6 in six weeks [108].

Adverse Events

Intraocular clindamycin has not demonstrated retinal toxicity in various studies and seems to be generally well tolerated in regards to side effect profile [108-110]. Administration through the intravitreal route avoids some side effects from systemic therapy, such as toxic megacolon and pseudomembranous colitis, yet it does not avoid the problem of drug sensitivity [112].

Intravitreal Injection of Trimethoprim/Sulfamethoxazole

Trimethoprim/Sulfamethoxazole (co-trimoxazole) 1.28 mg/0.08 mL has recently been suggested as an alternative treatment for intravitreal clindamycin for treatment of retinitis associated with toxoplasmosis. Co-trimoxazole, is a combination of two antimicrobial agents, trimethoprim and sulfamethoxazole, that act by inhibiting two successive steps of the *de novo* synthesis of tetrahydrofolate, the biologically active form of folic acid inside the organism. As each drug component of co-trimoxazole works on a different step of the folic acid cycle, a synergistic response against toxoplasmosis is achieved, and resistance is likely to develop more slowly than if each drug is administered alone. Soheilian et al. showed that clotrimazole treatment resulted in

resolution of all four cases in a case series using weekly or biweekly injection, without the need for systemic treatment [113]. More recently, intravitreal injection of co-trimoxazole combined with dexamethasone was used to treat recurrent toxoplasmosis retinitis in a prospective study of 13 patients and 13 eyes. Mean baseline Snellen visual acuity was 20/400 and improved to 20/63 on average, eight weeks after a single injection [114].

Adverse Events

There is only scarce literature on the safety of intravitreal co-trimoxazole in humans. However, in rabbit eyes, co-trimoxazole caused no clinical, electrophysiological or histological abnormalities when evaluated in one study [115]. In a small prospective cohort, patients treated with co-trimoxazole and dexamethasone were not shown to have any adverse effects [114].

Future Direction

Numerous innovative drug delivery products are now in developments with the aim of providing targeted treatment to the posterior segment while limiting the difficulties associated with frequent intravitreal injections. Of the delivery products currently under investigation, ones that could be used in treatment of intraocular infection in the future are long acting antimicrobial implants that can be injected in the outpatient setting and refillable surgical implants [116]. Delivery of antimicrobials through the sclera, using low-level electric current iontophoresis, could also be a promising and low-risk route for drug administrations in the future [117]. Additionally, there has been a recent interest in nano-carriers, which may be of benefit in treatment of intraocular infection. These nanoparticles deliver drugs to specific portions of the posterior segment. Nanoparticles also improve passage of larger, poorly water-soluble or unstable molecules and increase the time of contact between the intraocular drug and target tissues of the posterior segment [118]. Phase II studies have investigated the suprachoroidal space as a potential treatment modality for retinal vein occlusion and non-infectious uveitis [119, 120]. Utilizing triamcinolone in the SCS via a novel microneedle to treat posterior uveitis has garnered some success with good safety profile [119]. No studies have used this approach in treatment of endophthalmitis or other infectious causes to date.



Table 1: Important Characteristics of Commonly used Intravitreal Antimicrobial Drugs

Drug	Target site; mechanism of action	Recommended Dose	Vitreous half-life, in hours (model eye)	Spectrum of activity	Time for re-treatment if needed (hours)
Antibacterials					
Vancomycin ^{2, 120}	Cell wall; prevents polymerization of peptidoglycan	1.0-2.0mg/0.1mL	25-56 (rabbit)	Gram-positive bacteria	36-72
Ceftazidime ¹³⁴	Cell wall; inhibits the transpeptidase reaction	2.25mg/0.1mL	13.8 (rabbit)	Gram-negative bacteria including <i>Pseudomonas aeruginosa</i>	48-72
Amikacin ^{103,129}	Protein synthesis; binds to the 30s ribosomal subunit of bacteria	0.4mg/0.1mL	22.5 (rabbit)	Gram-positive cocci & gram-negative bacteria	36-60
Gentamycin ¹⁰³	Protein synthesis; binds to the 30s ribosomal subunit of bacteria	0.1mg/0.1mL	NA	Gram-positive cocci & gram-negative bacteria	NA
Moxifloxacin ^{79,84}	DNA: interferes with DNA gyrase and topoisomerase IV enzymes	0.5mg/0.1mL	1.72 (rabbit)	Gram-positive & gram-negative bacteria	12
Antifungals					
Amphotericin B ^{32,140,157}	Cell membrane; complexes with cell membrane ergosterol resulting in disturbed cell membrane function	0.05mg/0.1mL	25.5-56 (human)	Most yeasts & moulds	48
Voriconazole ^{23,71,107,139,140}	Cell membrane; interferes with ergosterol synthesis resulting in disturbed cell membrane function	0.1mg/0.1mL	2.5-6.5 (human)	Extended antifungal spectrum	24-48
Antivirals					
Ganciclovir ^{17,113,154}	DNA; selectively inhibits DNA polymerase in viral cells preventing DNA chain elongation	2mg/0.05mL	18.8 (human)	CMV. Also HSV & VZV	72*
Foscarnet ^{120,150}	DNA; inhibits DNA polymerase enzyme preventing DNA chain elongation	2.4mg/0.1mL	77 (rabbit)	HSV, VZV & CMV	72*
Antiprotozoals					
Clindamycin ^{10,126,144}	Protein synthesis; binds to the 50s ribosomal subunit of organism	1mg/0.1mL	40 (human)	<i>Toxoplasma gondii</i> . Also gram-positive cocci & anaerobes	72
Trimethoprim/sulfamethoxazole ³⁵	Metabolic pathways; inhibits the bacterial synthesis of tetrahydrofolic acid	1.28 mg/0.08 mL	NA	<i>Toxoplasma gondii</i> . Also gram-positive & negative bacteria	72

mg/ml: milligrams per milliliters; NA: not available; CMV: Cytomegalovirus; HSV: Herpes Simplex Virus; VZV: Varicella Zoster Virus.

* Treatment is used every 72 hours during the induction phase for about 2-3 weeks followed by weekly maintenance treatment.

CONCLUSION

Using the intravitreal route to administer antimicrobial drugs has been the standard approach for treatment of postoperative bacterial endophthalmitis, yet treatment of endogenous endophthalmitis, whether viral, fungal or bacterial, requires a multi-modality approach with intravitreal therapy being mainly used as an adjunctive to systemic antimicrobial treatment. While there has been recent interest in treating toxoplasma retinitis solely by intravitreal therapy instead of systemic antibiotics, there is still not enough evidence to support this approach for all patients. Table 1 outlines the important characteristics of commonly used intravitreal antimicrobial drugs, including mechanism of action, dosing, and half-life in the vitreous and spectrum of activity.

Intravitreal administration of antimicrobial drugs represents an important strategy in the armamentarium

for the treatment of infectious posterior uveitis. As the intravitreal route bypasses the blood ocular barriers, this route of administration allows rapid and direct drug delivery to the vitreous cavity at very high concentrations that exceeds the MIC of most organisms, while decreasing systemic sequelae. This is of utmost importance in eyes that are at imminent risk of developing severe visual loss due to macular or optic nerve involvement and in patients, who cannot tolerate systemic medications [13]. However, intraocular therapy can be associated with ocular toxicity, as the difference between the therapeutic and the toxic doses of some antimicrobial drugs falls within a narrow concentration range.

Method of Literature Search

This review was based mainly on recent literature during the last ten years with inclusion of some relevant older articles, particularly those related to drug



pharmacokinetics. In addition, case reports of a particular relevance were also reviewed. MEDLINE database search was conducted using the following key words alone and in various combinations: amikacin, amphotericin, caspofungin, ceftazidime, cefuroxime, choroiditis, cidofovir, ciprofloxacin, clindamycin, endophthalmitis, foscarnet, ganciclovir, gentamycin, herpes, intracameral, intraocular, intravitreal, moxifloxacin, pharmacodynamics, pharmacokinetics, quinolones, retinitis, suprachoroidal space, toxoplasma, traumatic, vancomycin, and voriconazole. Relevant articles only in English language were obtained and

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