

Topical azithromycin or ofloxacin for endophthalmitis prophylaxis after intravitreal injection

Pedro Romero-Aroca¹
Laura Sararols²
Lluís Arias³
Ricardo P Casaroli-Marano⁴
Francisca Bassaganyas⁵

¹Department of Ophthalmology, Hospital Universitari Sant Joan, Universidad Rovira i Virgili, Reus,

²Department of Ophthalmology, Hospital de Granollers, Granollers,

³Department of Ophthalmology, Hospital Universitari de Bellvitge, Barcelona, ⁴Instituto Clínico de Oftalmología, Hospital Clínic de Barcelona, Barcelona, ⁵Department of Ophthalmology, Hospital de la Sant Creu i Sant Pau, Barcelona, Spain

Background: The number of patients who have undergone intravitreal injections has increased enormously in recent years, but a consensus is still lacking on prophylaxis for endophthalmitis. The aim of this prospective, observational study was to evaluate the prophylactic effect of azithromycin eye drops versus ofloxacin eye drops.

Methods: The study was conducted in five hospitals in Spain and included all patients undergoing intravitreal injections of triamcinolone, bevacizumab, ranibizumab, or pegaptanib over one year. Patients received azithromycin 15 mg/g eye drops (twice daily on the day prior to injection and for another 2 days) or ofloxacin 3 mg/g eye drops (every 6 hours on the day prior to injection and for another 7 days).

Results: In the azithromycin group, there were 4045 injections in 972 eyes of 701 patients. In the ofloxacin group, there were 4151 injections in 944 eyes of 682 patients. There were two cases of endophthalmitis (0.049%) in the azithromycin group and five (0.12%) in the ofloxacin group. The odds ratio of presenting with endophthalmitis in the ofloxacin group compared with the azithromycin group was 2.37 (95% confidence interval [CI] 1.32–3.72, $P < 0.001$). There were two cases of noninfectious uveitis after triamcinolone injection in the azithromycin group (0.049%) and two (0.048%) in the ofloxacin group; no significant differences were observed (odds ratio 0.902, 95% CI 0.622–1.407, $P = 0.407$). Conjunctival hyperemia was observed in 12 cases in the azithromycin group and none in the ofloxacin group.

Conclusion: The risk of endophthalmitis was significantly greater with ofloxacin than with azithromycin. These findings provide a valuable addition to the ever-increasing pool of information on endophthalmitis prophylaxis after intravitreal injection, although further large-scale studies are required to provide definitive conclusions.

Keywords: endophthalmitis prophylaxis, intravitreal injections, azithromycin, ofloxacin, antibiotics

Introduction

The number of patients who have undergone intravitreal injections has increased enormously in recent years, partly due to the greater number of pathologies in which these injections are indicated (diabetic retinopathy, age-related macular degeneration, diabetic or retinal venous occlusion, macular edema, or uveitis) and partly because of the growing number of available drugs that can be administered in this way.¹ Intravitreal antibiotics were first used at the end of the 1990s and early in the new millennium, and new drugs are constantly being commercialized for intravitreal injection, such as corticosteroids and anti-vascular endothelial growth factor agents. In the coming years, more new drugs will likely become available; slow-release drugs such as fluocinolone

Correspondence: Pedro Romero-Aroca
Department of Ophthalmology, Hospital Universitari Sant Joan, Universidad Rovira i Virgili, Av del Dr Josep Laporte, 2 43204 Reus, Spain
Tel +34 977 310 300 ext 5308
Fax +34 977 323 754
Email romeropere@gmail.com

are already approved in some territories, and intravitreal implants are already under consideration. However, this increase in the number of intravitreal injections has also meant an increase in the number of complications, such as post-intravitreal injection endophthalmitis, over the past few years.²

Despite the existence of guidelines³ and a degree of conformity in procedures for intravitreal injection, differences between institutions and physicians⁴ have resulted in some variation in the rate of endophthalmitis; however, the most studies report rates in the range of 0.02%–0.3%.^{5–9}

Prophylaxis for postoperative endophthalmitis after cataract surgery has improved in recent years with the postoperative administration of eye drops (such as fourth-generation quinolones) or intracameral cephalosporin injection at the end of surgery.^{10–15} Conversely, information is lacking on postoperative endophthalmitis prophylaxis after intravitreal injections.^{16,17} Endophthalmitis is a relatively rare complication of intravitreal injection and so controlled clinical trials require large patient samples to provide definitive conclusions. At present, one approach for prophylaxis consists of instillation of povidone iodine into the conjunctival sac prior to injection, plus subsequent administration of antibiotic eye drops.¹⁸ The aim of this study was to evaluate the prophylactic effect of azithromycin versus ofloxacin eye drops against endophthalmitis after intravitreal injection.

Materials and methods

This prospective, observational study was conducted in five hospitals in Spain. The study population included all patients undergoing intravitreal injections of triamcinolone, bevacizumab, ranibizumab, or pegaptanib from January 2010 to December 2010. Patients undergoing ocular surgery or those allergic to quinolones or macrolides were excluded.

Prophylactic treatment

The prophylactic protocol consisted of topical povidone iodine 10% on the skin of the periorbital region plus 5% on the conjunctiva and eyelashes for a minimum of one minute. The periorbital region and eyelashes were draped and a sterile lid speculum, topical anesthetic, and sterile gloves were used. Patients were randomized to receive azithromycin 15 mg/g eye drops (twice daily on the day prior to injection and for 2 days post-injection) or ofloxacin 3 mg/g eye drops (every 6 hours on the day prior to injection and for another 7 days).

Standard operation procedures

After prophylactic measures, the injection was made at the temporal inferior quadrant 4 mm from the limbus. All patients were examined the day before injection.

Assessments

A total of eight follow-up visits every 6 weeks were scheduled. A complete ophthalmologic examination was performed at each visit. Vitreous samples were obtained by manual vitrectomy before intravitreal antibiotics in patients showing signs of acute endophthalmitis.

Definition of acute postoperative endophthalmitis

A diagnosis of presumed acute endophthalmitis was made by the ophthalmologist according to Endophthalmitis Vitrectomy Study criteria.¹⁹ All suspected cases had swollen eye lids, pain and an opaque vitreous.²⁰ If a positive culture of vitreous sample was obtained, the case was confirmed as acute endophthalmitis. The diagnosis of pseudoendophthalmitis secondary to intravitreal triamcinolone injection was based on decreased visual acuity, without pain and with minimal red eye that appeared 1–3 days after the injection, with hyalitis and a fibrinous reaction in the anterior chamber.

Microbiological methods

Vitreous samples obtained by the ophthalmologist were processed immediately. A Gram stain was performed and the sample cultivated in Petri dishes. Antibigram susceptibility testing was performed according to MENSURA (Mesa Española de Normalización de la Sensibilidad y Resistencia a los Antimicrobianos) criteria.^{21,22}

Statistical analyses

Statistical analyses were performed using SPSS statistical software version 17.0 (SPSS Inc, Chicago, IL). Values are expressed as the mean \pm standard deviation, and statistical analysis was determined using the Mann–Whitney *U* test.

Results

A total of 1383 patients were included. The mean patient age was 69.8 ± 7.55 (53–89) years in the azithromycin group and 68.17 ± 7.83 (53–90) years in the ofloxacin group ($P = 0.372$). Females accounted for 58% of patients in both groups. There were no statistically significant differences between the groups. The drugs injected in each group are shown in Table 1. Again, there were no statistically significant differences between the groups. In the azithromycin group, there were a total of

Table 1 Intravitreal injections and drugs administered

	Azithromycin (n = 4045)	Ofloxacin (n = 4151)
Ranibizumab	2648	2946
Bevacizumab	872	840
Pegaptanip	52	42
Triamcinolone	476	323

4045 injections in 972 eyes of 701 patients (4.16 injections per eye and 5.77 injections per patient). In the ofloxacin group, there were a total of 4151 injections in 944 eyes of 682 patients (4.39 injections per eye and 6.08 injections per patient).

Endophthalmitis cases

There were two cases (0.049%) of endophthalmitis (acute endophthalmitis and pseudoendophthalmitis) within a mean time of 4.37 ± 1.33 days after surgery in the azithromycin group and five cases (0.12%) within a mean time of 4.41 ± 1.29 days in the ofloxacin group. The characteristics of the seven cases are shown in Table 2. The risk (odds ratio) of presenting with endophthalmitis in the ofloxacin group compared with the azithromycin group was 2.37 (95% confidence interval [CI] 1.32–3.72, $P < 0.001$). When limiting the analysis to culture-positive cases (one case in the azithromycin group and three in the ofloxacin group), the estimated relative risk was 3.01 (95% CI 1.97–4.11, $P < 0.001$).

Adverse reactions

There were two cases of uveitis after triamcinolone injection in the azithromycin group (0.049%) and two cases (0.048%) in the ofloxacin group. No significant differences were observed in the statistical analysis (odds ratio 0.902, 95% CI 0.622–1.407, $P = 0.407$). No cases of raised intraocular pressure were recorded. The characteristics of the patients are shown in Table 3.

Table 2 Characteristics of patients with endophthalmitis

Gender	Age	Drug injected	Culture	Endophthalmitis treatment
Azithromycin (n = 2)				
Male	77	Ranibizumab	<i>S. epidermidis</i>	Intravitreal antibiotics
Female	80	Pegaptanip	Negative	Intravitreal antibiotics
Ofloxacin (n = 5)				
Male	76	Ranibizumab	<i>S. epidermidis</i>	Intravitreal antibiotics
Male	72	Ranibizumab	<i>S. epidermidis</i>	Intravitreal antibiotics + 25-gauge vitrectomy
Female	77	Ranibizumab	<i>S. aureus</i>	Intravitreal antibiotics
Female	69	Ranibizumab	Negative	Intravitreal antibiotics
Male	76	Ranibizumab	Negative	Intravitreal antibiotics

Abbreviations: *S. epidermidis*, *Staphylococcus epidermidis*; *S. aureus*, *Staphylococcus aureus*.

Table 3 Characteristics of patients with triamcinolone reaction

Gender	Age	Culture	Ocular pathology
Azithromycin (n = 2)			
Male	78	Negative	Diabetic macular edema
Female	82	Negative	Diabetic macular edema
Ofloxacin (n = 2)			
Female	71	Negative	Diabetic macular edema
Female	74	Negative	Diabetic macular edema

Other complications included conjunctival hyperemia (12 cases with azithromycin [0.29%] and none with ofloxacin), punctate keratitis (two cases with azithromycin and none with ofloxacin), subconjunctival hemorrhage (eight cases with azithromycin and six with ofloxacin) and a decrease in acute visual acuity with relapse a few minutes after intravitreal injection (three cases in each group).

Discussion

With the considerable growth in the use of intravitreal injections in recent years, there has been an increasing interest in determining an effective strategy for endophthalmitis prophylaxis.

The incidence of endophthalmitis, which is a potentially vision-threatening condition, is currently unclear because very few studies have been conducted. Most data are derived from extended clinical trials that attempted to administer drugs intravitreally, such as the RESTORE (Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema) study, in which no endophthalmitis cases were observed after 2415 injections²³ or the Diabetic Retinopathy Clinical Research Network²⁴ study in which one patient (0.9%; 95% CI 0.02–4.7) developed endophthalmitis after receiving ranibizumab. According to the meta-analysis by Jager et al,¹⁸ the incidence of endophthalmitis after use of intravitreal medicines is 0.3% per injection and 0.9% per eye. The Vitravene Study Group²⁵ described two cases of endophthalmitis after 1791 injections (0.11%) in 330 eyes (0.60%).

A larger study was performed by McCannel et al²⁶ who conducted a meta-analysis of the US literature from 2005 to 2009 and observed a total of 52 cases of endophthalmitis in 105,536 injections, with an incidence of 0.049% (95% CI 0.038–0.065). In this study, endophthalmitis culture was negative in 24 cases (48.0% [95% CI 34.8–61.5]) and positive in 26 (52% [95% CI 38.5–65.2]). Of the 26 culture-positive isolates, the causative organisms were coagulase-negative *Staphylococcus* spp. in 17 cases (65.4% [95% CI 46.0–80.6]), *Streptococcus* spp. in eight cases

(30.8% [95% CI 16.5–50.2]), and *Bacillus cereus* in one case (3.8% [95% CI 0.9–19.0]). The authors found a significantly higher number of cases due to *Streptococcus* species than after cataract surgery in the Endophthalmitis Vitrectomy Study. The percentage of cases with endophthalmitis in the current study was similar to that in the published data, at 0.049% in the azithromycin group and 0.12% in the ofloxacin group. Unlike McCannel et al,²⁶ the most commonly found bacterium (three of the four positive cases) in our study was *Staphylococcus epidermidis*.

Because little is known about the incidence of endophthalmitis, it is unclear whether prophylactic antibiotics should be used. Some authors, such as Bhatt et al,²⁷ concluded that “the rate of endophthalmitis after intravitreal injections administered in a clinical practice setting when aseptic technique is used is similar with or without the use of post injection antibiotics”, but their study was based on a small number of patients. In contrast, most scientific bodies recommend the use of topical antibiotics in addition to prophylactic measures during surgery such as povidone iodine instillation on the conjunctiva, draping of the periorbital region and eyelashes, and the use of a sterile lid speculum. However, there are few recommendations on antibiotic use. The Royal College of Ophthalmologists²⁸ recommends a dose of antibiotics before injecting the drug, while the Spanish Society of Retina and Vitreous recommends topical antibiotic treatment after injection.²⁹ The French Agence Nationale de Sécurité du Médicament also recently recommended topical antibiotics after injection, but stated that systemic administration is not indicated.³⁰ They advised referring to the marketing authority for the substance being injected for advice on preinjection topical antibiotic prophylaxis.

Azithromycin was chosen for this study because it is a broad spectrum antibiotic that covers most commonly found bacteria in the environment and is more potent against most Gram-negative organisms than erythromycin.^{31,32} Furthermore, adequate and long-lasting levels were observed in the conjunctiva that remained well above the minimum inhibitory concentration (MIC) breakpoint for susceptible organisms for up to 24 hours after instillation. Residual azithromycin levels observed 7 days after the last administration were above the MIC breakpoint of 0.5 µg/g in the conjunctiva and cornea. This permits topical administration twice daily for 3 days, resulting in significant concentrations in the conjunctiva and cornea for at least 7 days after final administration.^{33,34} Although azithromycin has poor intraocular penetration when given topically, its main role is via the elimination of periocular bacteria.

In the current study, we observed that the number of endophthalmitis cases was higher in the group that used ofloxacin (0.12%) versus the azithromycin group (0.049%), resulting in a significantly increased risk of endophthalmitis of 2.37 ($P < 0.001$). However, the relatively low sample size and incidence of endophthalmitis is one of the major limitations of the study that precludes any categorical confirmation of the advantage of one drug over the other in the prophylaxis of endophthalmitis after intravitreal injection. Azithromycin-treated patients had a somewhat higher rate of conjunctival hyperemia, that was nevertheless seen in less than three cases per 1000. There were no differences in other adverse events.

In conclusion, these findings provide a valuable addition to the ever-increasing pool of information on endophthalmitis prophylaxis after intravitreal injection, although further similar large-scale studies will be required before reaching definitive conclusions.

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Disclosure

The authors report no conflicts of interest in this work.

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