MEGA JOURNAL OF CASE REPORTS

OPEN ACCESS

Research Article

Compiled Date: July 03, 2024

Efficacy of Azithromycin Hydrate Ophthalmic Solution for Meibomitis-Related Keratoconjunctivitis

Sho Ishikawa, MD, PhD*, Yasuhito Narita, MD and Kei Shinoda, MD, PhD

Department of Ophthalmology, Saitama Medical University, Japan

***Corresponding author**: Sho Ishikawa, Department of Ophthalmology, Saitama Medical University, 38 Morohongo, Moroyama, Saitama 350-0495, Japan, Tel: +81-4-9276-1250; Fax: +81-4-9295-8002

Abstract

Purpose: Meibomitis-related keratoconjunctivitis (MRKC) is generally treated with a combination of antibacterial eye drops and low-concentration steroids. Azithromycin hydrate ophthalmic solutions exhibit antibacterial and anti-inflammatory effects. In the present study, we investigated the efficacy of azithromycin hydrate ophthalmic solution monotherapy for MRKC.

Methods: Based on their medical records, patients with MRKC who visited Saitama Medical University Hospital between January 2020 and August 2022 and were treated with azithromycin eye drops as a single agent were retrospectively evaluated for improvement of hyperemia and corneal lesions.

Results: Eight patients (2 males and 6 females) with a total of 8 eyes, and a mean age of 39.5 ± 26.1 years, were included in the study. Six patients had phlyctenular-type MRKC, and two had non-phlyctenular-type MRKC. The bulbar conjunctival hyperemia grade improved from 1.9 ± 0.6 before treatment to 0.8 ± 1.0 after treatment. The conjunctival vascular area in the surrounding 2 mm annulus from the cornea improved from 51.9 ± 18.5 before treatment to 26.2 ± 27.4 after treatment. Seven patients (88%) showed an improvement in at least one grade. All patients complied with the frequency of eye drops, and there were no apparent adverse effects.

Conclusions: Azithromycin ophthalmic monotherapy may be effective in the treatment of MRKC.

Keywords: Azithromycin; Phlyctenular keratoconjunctivitis; Meibom gland dysfunction; Meibomitis-related keratoconjunctivitis; MRKC

Introduction

Phlyctenular keratoconjunctivitis is a nodular inflammation of the cornea or conjunctiva resulting from a hypersensitive reaction to foreign antigens. McCulley et al. first reported that meibomian keratoconjunctivitis is characterized by excessive or stagnant meibomian secretions, superficial punctate keratopathy that preferentially affects the lower intervertebral part of the cornea, and bulbar conjunctival injection [1]. Suzuki et al. reported meibomian gland inflammation associated with an ocular surface inflammatory disease called Meibomitis-Related Keratoconjunctivitis (MRKC). MRKCs are classified as phlyctenular or non-phlyctenular [2]. The non-phlyctenular type of MRKC tends to be more common in elderly patients with no nodular inflammation of the corneal lesions but with prominent superficial punctate keratopathy.

The first-line treatment for phlyctenular and non-phlyctenular keratoconjunctivitis aims to decrease the inflammatory response. Phlyctenulosis generally responds to topical steroids [3]. In addition to treating the inflammation, it is important to reduce the sources of antigens that induce it. The pathogenesis of MRKC has been linked to *S. aureus* [4,5] and *C. acnes* [6,7]. *C. acnes* normally inhabits human sebaceous follicles and plays a central role in the development of inflammatory lesions [8]. Treating pathogens in patients with MRKC involves systemic and topical cephalosporins to eliminate or reduce *C. acnes* infections [7, 9].

Azithromycin is a macrolide antibacterial characterized by a broad antibacterial spectrum, a long half-life due to its tissue and cell penetration [10], and anti-inflammatory properties [11]. 1.5 Azithromycin eye drops (1.5 %) and lid hygiene have been effective in treating ocular rosacea with phlyctencular blepharokeratoconjunctivitis [12] and meibomian gland dysfunction [13]. Azithromycinhydrate ophthalmic solution (Azimycin ophthalmic solution 1%®, Senju Pharmaceutical) was introduced in Japan in September 2019. Several reports have demonstrated the efficacy of azithromycin hydrate ophthalmic solution in treating blepharitis [14,15] and MRKC [16]. However, to the best of our knowledge, there has been only one report on the treatment of MRKC. Therefore, we evaluated the efficacy of a 1% azithromycin hydrate ophthalmic solution for the treatment of MRKC.

Materials and Methods

Participants

Institutional Review Board/Ethics Committee approval was obtained from the Ethics Committee of Saitama Medical University Hospital (2023-034). This study adhered to the tenets of the Declaration of Helsinki. The need for written informed consent was waived by the Ethics Committee of Saitama Medical University owing to the retrospective design of the study. We retrospectively enrolled eight patients diagnosed with MRKC who were treated with azithromycin hydrate ophthalmic solution monotherapy at Saitama Medical University Hospital between January 2020 and August 2022. Patients Pho had been previously prescribed azithromycin hydrate ophthalmic solution or oral azithromycin, or who were not diagnosed within 2 weeks, were excluded. We categorized the causes of MRKC into phlyctenular and non-phlyctenular types. We diagnosed the phlyctenular type with one or more nodular inflammations of the cornea, and the non-phlyctenular type with superficial punctate corneal lesions without nodular inflammation of the cornea. Treatment with azithromycin hydrate ophthalmic

solution was initiated twice daily for 2 days, then decreased to once daily for 12 days in all patients. None of the patients received any other treatments, including topical antibiotics or steroids. Additionally, none of the patients met the criteria for dry eye [17]. Demographic and clinical characteristics of the patients, including age, sex, changes in the corneal ulcer, and hyperemia of the conjunctiva before and after 14 days of treatment, were collected from their medical records.

Conjunctival Hyperemia Assessment Method

Conjunctival hyperemia was evaluated both qualitatively and quantitatively. Hyperemia of the bulbar conjunctiva was classified as follows: 3, severe vasodilation of all vessels; 2, moderate dilation of many vessels; 1, mild dilation of several vessels; and 0, no manifestations [18]. Conjunctival grading was performed by two examiners (S. I. and Y. N.). Efficacy was defined as the improvement of at least one conjunctival hyperemia grade or achieving grade 0. We calculated the percentage of the conjunctival vascular area in the 2–3 mm annulus surrounding the cornea. Photographs of the keratoconjunctiva taken before and after treatment were used for the analysis. After adjusting the magnification of the photographs so that the size of the cornea was the same, the conjunctival vessels and conjunctiva were separated from the conjunctiva via binarization. The binarization method was as follows: import the photo into Image J software, set the brightness and contrast, adjust the color of the bulbar conjunctiva and the vessels, and set the color threshold. Binarization was performed using the set color threshold values to separate the bulbar conjunctiva into white and the conjunctival vessels into black. The area of blood vessels in the conjunctiva was measured using ImageJ's particle analysis command for the conjunctival vascular area in the 2–3 mm annulus surrounding the cornea **(Figure 1).**

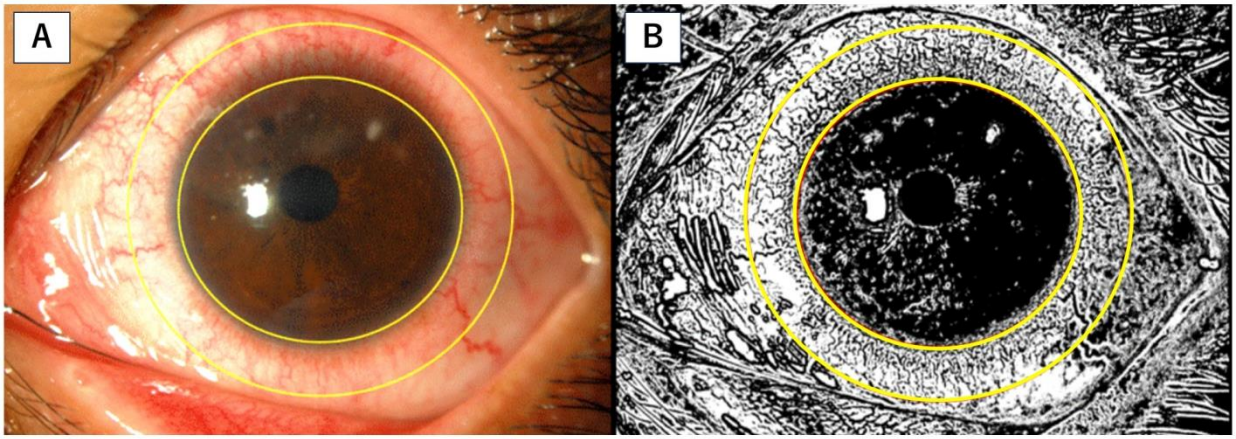

Figure 1: Photograph of pre and post-binarization. (A) The photograph of 23 years-old female phlyctenular patient. We calculated the percentage of conjunctival vascular area in the surrounding 2–3 mm annulus from the cornea (yellow circle). (B) Photographs of after binarization. The percentage of the conjunctival vascular area (black area) in the surrounding 2–3 mm annulus from the cornea (yellow circle) was 65.37%.

Statistical analyses

All statistical analyses were performed using JMP version 16® software (SAS Institute, Tokyo, Japan). All data are expressed as means ± standard deviation. The conjunctival hyperemia score and the conjunctival vascular area surrounding the 2–3 mm annulus from the cornea were compared pre- and post-treatment using the Wilcoxon signed rank test. Statistical significance was set at $p< 0.05$.

Results

Table 1 shows the variables before and after azithromycin hydrate ophthalmic solution monotherapy. The score of conjunctival hyperemia (1.9±0.6) significantly improved after treatment (0.8±1.0) (p=0.02). The conjunctival vascular area in the surrounding 2–3 mm annulus from the cornea significantly improved from 51.9 ± 18.5 before treatment to 26.2 ± 27.4 after treatment (p=0.04). Six patients had phlyctenular MRCK, and two had non-phlyctenular MRCK. All patients, except one with non-phlyctenular MRCK, showed qualitative and quantitative improvement in conjunctival hyperemia, and corneal infiltration disappeared. All patients with phlyctenula showed improved corneal nodular inflammation **(Figure 2)**.

Table 1: Profile of patients.

			Conjunctive hyperemia grade		Percentage of conjunctival vascular area (%)	
age	sex	Type of MRKC	pre	post	pre	post
13	female	phlyctenular	2	0	55.83	3.06
17	female	phlyctenular	1	0	53.13	18.72
22	female	phlyctenular	2	1	65.37	25.16
23	female	phlyctenular	2	0	65.37	15.15
41	female	non-phlyctenular	1	0	9.6	1.5
45	male	phlyctenular	2	1	61.58	32.34
72	female	phlyctenular	2	1	44.3	25.1
83	male	non-phlyctenular	3	3	60.21	88.65

MRKC; meibomitis-related keratoconjunctivitis

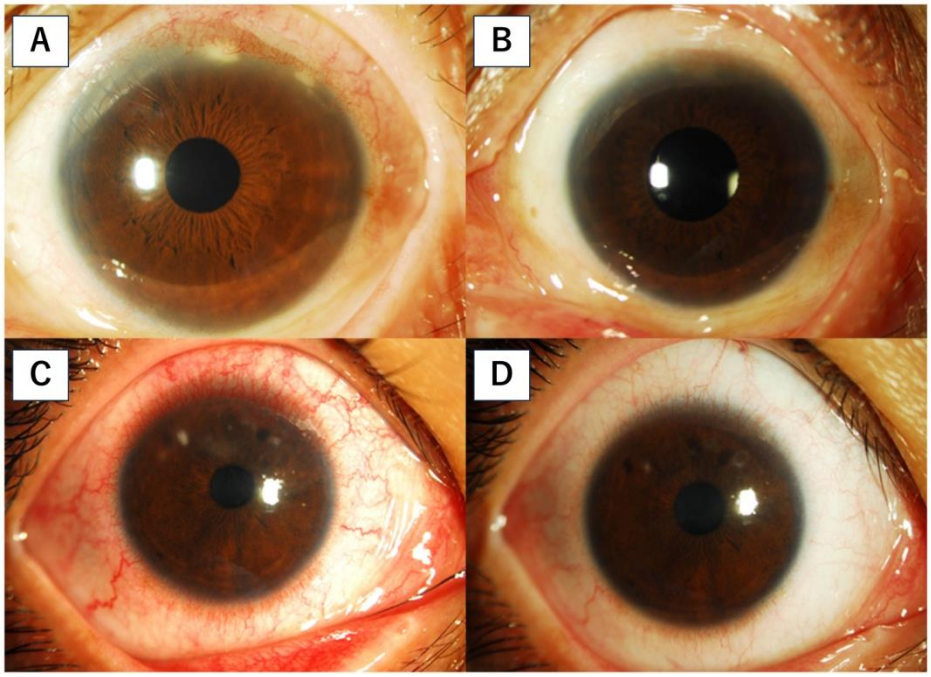

Figure 2: Photograph of patient's pre and after-treatment.

(A) The pre-treatment photograph of 72 years-old female phlyctenular patient. Nodular inflammation of the cornea was observed superior and superior temporal cornea. (B) The corneal nodular region disappeared and conjunctival hyperemia was improved after treatment. (C) The pre-treatment photograph of 22 years-old female phlyctenular patient. Nodular inflammation of the cornea was observed superior nasal and superior temporal of the cornea. (D) The corneal nodular region and conjunctival hyperemia were improved after treatment.

No patient discontinued azithromycin eye drops due to severe eye irritation in this study.

Discussion

In the present study, we showed that a single treatment with azithromycin hydrate ophthalmic solution for 14 days significantly improved conjunctival hyperemia and corneal infiltration. The azithromycin hydrate ophthalmic solution used in this study contained polycarbophils. In a previous report, the effect of azithromycin ophthalmic drops without polycarbophils was prolonged, from 3 to 10 months [12]. In an experiment where 1% azithromycin ophthalmic drops containing polycarbophils were administered to rabbits, azithromycin was rapidly distributed in the eyelids, reaching peak concentrations by the end of the 7-day treatment and was eliminated with a half-life of 125 h [10]. Due to the prolonged action of azithromycin hydrate ophthalmic solution, we believe that even 14-day treatment duration was effective in this study. Azithromycin exerts immunomodulatory effects on chronic inflammatory disorders [19]. Azithromycin-stimulatory effects on immune and epithelial cells, involving interactions with phospholipids and Erk1/2, are followed by the modulation of transcription factors AP-1, NFkappaB, inflammatory cytokines, and mucin release [19]. The first line of treatment for phlyctenular and non-phlyctenular MRKC is to

decrease the inflammatory response; therefore, we speculated that the immunomodulatory effects of azithromycin might be effective. In this study, azithromycin hydrate ophthalmic solution improved the signs of inflammation. In a previous study involving seven patients with phlyctenular and six with non-phlyctenular MRKC treated with azithromycin hydrate ophthalmic solution, the conjunctival score for the phlyctenular type (2.0±0.8) significantly improved after treatment (1.1±0.8) (p=0.03) **[16]**. Similar results were observed for conjunctival hyperemia scores in our study. We also conducted a qualitative evaluation of conjunctival hyperemia using ImageJ software. Yoneda et al. reported that the percentage coverage of blood vessels calculated using hyperemia analysis software correlated with the arithmetic average of clinical conjunctival hyperemia grading **[20].** According to the package insert, azithromycin hydrate ophthalmic solution causes eye irritation in less than 5% of cases and petechial keratitis and blepharitis in less than 1% of cases. None of the patients experienced any adverse reactions.

The present study has some limitations. Firstly, it was a relatively small, retrospective, single-center case series. More extensive studies are needed for an in-depth characterization of MRKC treatment. Secondly, the recurrence rate of MRKC remains unknown. Although we confirmed the absence of recurrence during the first 6 months after treatment in this retrospective study, the long-term duration beyond that periodis uncertain.

Conclusions

We demonstrated the efficacy of azithromycin hydrate ophthalmic solution monotherapy for treating MRKC. Conjunctival hyperemia and corneal infiltration improved after 14 days of treatment with azithromycin hydrate ophthalmic solution.

References

1. McCulley JP, Sciallis GF. Meibomian keratoconjunctivitis. Am J Ophthalmol. 1977;84(6):788-93.
2. Suzuki T. Inflamed Obstructive Meibomian Gland Dysfunction Causes Ocular Surface Inflammation. Invest Ophthalmol Vis Sci. 2018;59(14):DES94-DES101.
3. Thygeson P. The etiology and treatment of phlyctenular keratoconjunctivitis. Am J Ophthalmol. 1951;34(9):1217-36.
4. Smolin G, Okumoto M. Staphylococcal blepharitis. Arch Ophthalmol. 1977;95(5):812-6.
5. Zaidman GW, Brown SI. Orally administered tetracycline for phlyctenular keratoconjunctivitis. Am J Ophthalmol. 1981;92(2):178-82.
6. Kligman AM. An overview of acne. J Invest Dermatol. 1974;62(3):268-87.
7. Suzuki T. Meibomitis-related keratoconjunctivitis: implications and clinical significance of meibomian gland inflammation. Cornea. 2012;31:S41-4.
8. Dougherty JM, McCulley JP. Bacterial lipases and chronic blepharitis. Invest Ophthalmol Vis Sci. 1986;27(4):486-91.
9. Suzuki T, Mitsuishi Y, Sano Y, Yokoi N, Kinoshita S.Phlyctenular keratitis associated with meibomitis in young patients. Am J Ophthalmol. 2005;140(1):77-82.
10. Akpek EK, Vittitow J, Verhoeven RS,

Brubaker K, Amar T, Powell KD, et al. Ocular surface distribution and pharmacokinetics of a novel ophthalmic 1% azithromycin formulation. J Ocul Pharmacol Ther. 2009;25(5):433-9.
11. Murphy BS, Sundareshan V, Cory TJ, Hayes D Jr, Anstead MI, Feola DJ. Azithromycin alters macrophage phenotype. J Antimicrob Chemother. 2008;61(3):554-60.
12. Doan S, Gabison E, Chiambaretta F, Touati M, Cochereau I. Efficacy of azithromycin 1.5% eye drops in childhood ocular rosacea with phlyctenular blepharokeratoconjunctivitis. J Ophthalmic Inflamm Infect. 2013;3(1):38.
13. Ciloglu E, Özcan AA, Incekalan T, Unal F. The Role of Topical Azithromycin in the Treatment of Meibomian Gland Dysfunction. Cornea. 2020;39(3):321-4.
14. Arita R, Fukuoka S. Efficacy of Azithromycin Eyedrops for Individuals With Meibomian Gland Dysfunction-Associated Posterior Blepharitis. Eye Contact Lens. 2021;7(1):54-59.
15. Nejima R, Eguchi H, Todokoro D, Inoue T, Kaji Y, Suzuki T et al. Analysis of treatment protocols using azithromycin eye drops for bacterial blepharitis: second report-bacteriological investigation. Jpn J Ophthalmol. 2022;66(6):579-89.
16. Shimizu Y, Shinji K, Mitoma K, Kiuchi Y, Chikama T. Efficacy of azithromycin hydrate ophthalmic solution for the treatment of internal hordeolum and meibomitis with or without phlyctenular keratitis. Jpn J Ophthalmol. 2023;67(5):565-9.
17. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, et al. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017;15(3):276-83.
18. Takamura E, Uchio E, Ebihara N, Ohno S, Ohashi Y, Okamoto S. Japanese guidelines for allergic conjunctival diseases 2017. Allergol Int. 2017;66(2):220-9.
19. Parnham MJ, Erakovic Haber V, Giamarellos-Bourboulis EJ, Perletti G, Verleden GM, Vos R. Azithromycin: mechanisms of action and their relevance for clinical applications. Pharmacol Ther. 2014;143(2):225-45.
20. Yoneda T, Sumi T, Hoshikawa Y, Kobayashi M, Fukushima A. Hyperemia Analysis Software for Assessment of Conjunctival Hyperemia Severity. Curr Eye Res. 2019;44(4):376-80.

Citation of this Article

Ishikawa S, Narita Y and Shinoda K. Efficacy of Azithromycin Hydrate Ophthalmic Solution for Meibomitis-Related Keratoconjunctivitis. Mega J Case Rep. 2024;7(7):2001-2009.

Copyright