Original research article

EJO European Journal of Ophthalmology

Treatment of *Acanthamoeba* keratitis with high dose PHMB (0.08%) monotherapy in clinical practice: A case series

European Journal of Ophthalmology
1–7

DOI: 10.1177/11206721241299470
journals.sagepub.com/home/ejo
Sage

Antonella Franch[1], Karl Anders Knutsson[2], Emilio Pedrotti[3], Adriano Fasolo[3,4], Federico Bertuzzi[2], Federica Birattari[1], Erika Bonacci[3], Pia Leon[1] and Vincenzo Papa[5]

Abstract

Objectives: *Acanthamoeba* keratitis (AK) is a rare sight-threatening infectious disease with no approved pharmacological treatments**.** Topical polihexanide 0.8 mg/ml (PHMB 0.08%) completed a pivotal clinical trial showing a medical cure rate of 84.9%. The purpose of this study is to evaluate the efficacy and safety of PHMB 0.08%, given as monotherapy, in clinical practice.

Methods: consecutive cases of AK were included. Diagnosis was confirmed by *in vivo* confocal microscopy or PCR. Patients were treated with PHMB 0.08% as part of a name-based compassionate use program. Treatment delivery frequency and termination were as advised in the pivotal clinical trial. Medical cure was defined as clinical evidence of healed epithelium and absence of corneal inflammation lasting 3 months after discontinuing all treatments.

Results: twelve eyes of 11 contact lens wearers with AK of variable severity were evaluated. Eleven of 12 (91.7%) eyes achieved a medical cure with no surgery. One eye had a corneal perforation and required emergency therapeutic keratoplasty. The median time of treatment with PHMB 0.08% was 100 days (range 35–222). Seven eyes (58.3%) reached a final visual acuity of 20/50 Snellen or better. Two subject reported worsening of conjunctival hyperaemia during the intensive phase of the treatment. No other adverse drug reactions were observed.

Conclusion: topical treatment with PHMB 0.08% monotherapy successfully cured AK in 11 of 12 eyes when used in real-world clinical practice, thereby confirming that results observed in the clinical trial could be obtained in this setting.

Keywords

Examination techniques, confocal microscopy, CORNEA / EXTERNAL DISEASE, acanthamoeba keratitis, CORNEA / EXTERNAL DISEASE, pharmacology, PHARMACOLOGY, anti-Infective agents, CORNEA / EXTERNAL DISEASE, corneal transplantation, CORNEA / EXTERNAL DISEASE

Date received: 30 April 2024; accepted: 28 October 2024

Introduction

Acanthamoeba keratitis (AK) is a rare sight-threatening ocular infection that occurs primarily in contact lens wearers. The estimated population incidence per year is 1–3 cases/million,[1,2] while amongst contact lens wearers the incidence is 20–50 cases/million.[2–4] There is currently no approved pharmacological treatment for AK. Available options are off-label antiseptic products, the most used being biguanides (polihexanide [PHMB] or

[1]Ophthalmic Unit, Ospedale SS Giovanni e Paolo, Venice, Italy
[2]Corneal and Ocular Surface Unit, San Raffaele Scientific Institute, Milan, Italy
[3]Ophthalmic Unit, University Eye Clinic, Verona, Italy
[4]Research Unit, Veneto Eye Bank Foundation, Mestre, Italy
[5]Medical Affairs, SIFI SpA, Aci.S.Antonio, Catania, Italy

Corresponding author:
Vincenzo Papa, Medical Affairs SIFI SpA, Via Ercole Patti 36, 95020 Aci S.Antonio (CT), Italy.
Email: vincenzo.papa@sifigroup.com

chlorhexidine), which are given alone or in combination with a diamidine 0.1% (propamidine or hexamidine).[5–8]

Until 2023 only two prospective randomized trials had been reported in patients with AK[9,10] providing insufficient evidence to evaluate the relative effectiveness and safety of medical therapy for the treatment of AK.[11] The expected outcome of actual treatments can be derived from the three largest retrospective case series (more than 500 eyes in total) reporting a medical cure rate of approximately 60%[4,12,13] and a poor outcome (low vision and/or surgery) in 40% of subjects.[12] Therapeutic keratoplasty is usually limited to severe or progressive cases not responsive to medical treatment and this occurs in approximately 25% of patients.[14,15] Polihexanide 0.8 mg/ml (PHMB 0.08%), a recently developed preservative-free ophthalmic solution, was successfully studied in a randomized clinical trial using a detailed treatment delivery protocol (ClinicalTrials.gov: NCT03274895).[16] The medical cure rate without surgery was 84.9% with a median time-to-cure of 147 days. Therapeutic keratoplasty was necessary in 7.8% eyes and toxicity was reported in 1.5% cases.[16] This product has been made available by the Manufacturer (SIFI S.p.A., Italy) in several EU countries before the marketing authorization through a name-based compassionate use program.

We describe here clinical characteristics and outcomes of a series of consecutive patients with AK who entered in the compassionate use program in 3 referral corneal centres in Italy with the purpose to provide information on clinical effectiveness and safety of PHMB 0.08% when used in a real-life clinical practice setting.

Methods

This was a clinical chart review of consecutive patients with AK treated from January to July 2023 with PHMB 0.08% at 3 cornea centres in Italy (SS Giovanni and Paolo Hospital and Veneto Eye Bank Foundation-Venice, San Raffaele Scientific Institute-Milan, and the University of Verona). Patients were previously included in a name-based compassionate use program approved by the Italian Medicine Agency (AIFA) in 2022. A written informed consent was obtained before the participation in the program and the treatment of each patient was approved by a local Ethics Committee. Demographic data were anonymized.

An AK diagnosis was suspected on clinical findings and confirmed by *in vivo* confocal microscopy (IVCM) and, when available, by polymerase chain reaction (PCR). AK was classified into 3 stages, as described by Robaei.[17]

Patients were given hourly drops of PHMB 0.08% (daytime only) for 5 days; after which the treatment was tapered off to every 2 h for 1 week, then to every 3 h for additional 7 days and finally to four times a day until cured. This was the protocol recommended for the use of this drug in the phase 3 trial.[16] All patients underwent a complete ophthalmic examination according to routine procedures of each cornea centre. Criteria for the use of concomitant medications (as corticosteroids or antibiotics) were not set in advance and each physician established their use on an individual basis. Patients were evaluated on weekly or monthly basis according to routine procedures of each centre. Medical cure was defined as clinical evidence of elimination of *Acanthamoeba* (healed epithelium and absence of corneal inflammation) maintained for at least 3 months after discontinuing all pharmacological treatments, with no surgery or switch to another anti-amoebic product.[16]

Results

Eleven patients wearing contact lens diagnosed with AK were treated with of PHMB 0.08% as monotherapy. One subject had a bilateral infection. Patient demographics, clinical characteristics, and outcomes are summarised in Table 1 and listed in Table 2.

All patients showed typical clinical findings of AK. Purely epithelial disease (Stage-1) was encountered in 2 patients and 6 had advanced (Stage-3) disease including corneal ring infiltrates, severe inflammation or hypopyon. Most patients had low vision; only 3 patients had a visual acuity $\geq$ 20/50 Snellen at presentation. Pain was present in 8/11 (72.7%) patients.

PHMB 0.08% treatment resulted in complete corneal healing with resolution of ocular inflammation in 11/12 eyes (91.7%). Adjunctive therapy with topical steroids was given to 3/12 eyes (25.0%) while topical antibiotics were used in 8/12 eyes (66.7%). No relapse was observed after a follow-up off-treatment of 3 months. Images from 3 representative cases are shown in Figure 1. A patient with an advanced disease underwent to an emergency keratoplasty due to corneal melting and perforation during the first month of therapy with PHMB 0.08%; after an additional treatment with PHMB 0.08% (2 months) and 2 further months off-therapy, the disease was considered resolved. The mean (SD) duration of treatment was 101 (51) days (median 100, range 35–222 days). A final visual acuity of 20/50 Snellen or better was measured in 7 patients while 4 had visual acuity less than 20/100 due to residual central cornea leucoma.

A moderate to severe temporary conjunctival hyperaemia was detected in 2 patients during the intensive phase of treatment; for one of them this event was likely due to anti-amoebic drug toxicity. No additional adverse drug reactions were recorded.

Discussion

There is no recognized standard of care for the medical treatment of AK in any country. Current first-line agents

Table 1. Summary table of cases with Acanthamoeba keratitis treated with PHMB 0.08%.

Patients	n = 11	Eyes	n = 12
Sex (n, %)		**Diagnosis (n, %)**	
Male	4 (36%)	IVCM alone	7 (58%)
Female	7 (64%)	IVCM + PCR	5 (42%)
Age (years)		**BCVA (Snellen) at baseline (n, %)**	
Mean (SD)	41.4 (19.5)	≤20/100	9 (75%)
Range	17–67	≥20/50	3 (25%)
Time from onset of symptoms		**Disease stage (n, %)**[2]	
< 21 days	6 (55%)	I	2 (17%)
>21 days	5 (45%)	II	4 (33%)
		III	6 (50%)
Previous topical treatment (n, %)		**Duration of treatment with PHMB 0.08% (days)**	
Corticosteroids[1]	10 (91%)	Mean (SD)	101 (51)
Antibiotics	8 (73%)	Median	100
Anti amoebics (chlorhexidine, PHMB 0.02%)	3 (27%)	Range	35–222
		Concomitant topical treatments (n, %)	
		Corticosteroids	3 (25%)
		Antibiotics	8 (67%)
		None	2 (17%)
		Clinical resolution (n, %)[3]	
		Yes (cured)	11 (92%)
		No (surgery)	1 (8%)
		BCVA (Snellen) at the end of treatment (n, %)	
		≤20/100	5 (42%)
		≥20/50	7 (58%)

[1]Corticosteroids were discontinued in all patients before starting PHMB 0.08%.
[2]Stage of disease (*Robaei et al. 2014*).
[3]Confirmed 3 months off-treatment with no sign of a recurrence.
IVCM = in vivo confocal microscopy; BCVA = best corrected visual acuity; PCR = polymerase chain reaction.

are unlicensed biguanides (chlorhexidine, PHMB) often compounded and used in combination with diamidines (propamidine, hexamidine).[8] In addition, the treatment delivery protocol for these antiseptics is not standardized and remains empirical.

A novel preservative-free ophthalmic solution containing PHMB 0.08% successfully completed a phase 3 randomized clinical trial using a detailed treatment protocol. In that trial, 84.9% of patients (adjusted to 86.7% for baseline imbalance in covariates affecting outcomes) treated with PHMB 0.08% monotherapy reached a medical cure within 12 months from randomization.[16] These results are the best reported and much higher than those described in recently reported retrospective studies conducted in the EU and US including more than 500 cases of AK.[4,12,13] Since the detailed drug delivery protocol and the tight monitoring typical of clinical trial may have accounted for the improvement in outcomes,[16] it is important to understand if these results are transferable to real-world clinical practice.

This is the first case series of patients with AK treated with PHMB 0.08% outside a clinical trial setting. Since IVCM exhibits higher specificity and sensitivity than culture and PCR,[18] this technique was used to confirm clinical diagnosis of AK, whereas, as in the clinical trial,[16] AK resolution was a pure clinical judgement (healed epithelium and absence of corneal inflammation) because a negative IVCM may be insufficient to provide certainty of a cure.[19]

It is well recognised that poor outcomes of AK are associated with delayed diagnosis, use of steroids before anti-amoebic therapy and severity of disease at presentation.[3,5,17,20] Our series had several risk factors predictive of a negative outcome; indeed, 6 eyes had an advanced stage of disease (Stage 3) at presentation, 5 eyes a delay in the anti-amoebic treatment >3 weeks from symptom onset and 10 eyes received steroids before starting PHMB 0.08%. Despite these poor prognosis parameters at baseline, the overall medical cure rate obtained using PHMB 0.08% was high (91.7%) and comparable to that reported in the clinical trial (84.9%; 95% CI = 73.9–92.5).[16] As expected, the duration of treatment was highly variable ranging from 35 to 222 days with a median of 100 days; this is comparable with that reported in the clinical trial (146 days) with a Q1, Q3 (interquartile range) of 94, 217 days indicating that 25% of cases were cured in under 94 days and 25% over 217 days. PHMB 0.08% was used as monotherapy and administered in the daytime only (i.e., no administration during the night was required), which may improve patient's

Table 2. List of patients with Acanthamoeba keratitis treated with PHMB 0.08%.

Case no.	Symptoms onset (days)	Diagnosis	Initial BCVA	Previous treatments	Signs and symptoms	AK stage[2]	Duration of treatment with PHMB 0.08%(days)	Concomitant topical treatments	Final outcome[2]	Final BCVA
1 RE	>21	IVCM/ PCR	CF	Steroids and antibiotics. Antivirals (systemic)	Epithelial defects, ulcerations, corneal ring infiltrates.	3	222	Antibiotics	Cured	CF
1 LE		IVCM	CF		Epithelial defects, ulcerations, corneal ring infiltrates, corneal neovascularization	3	222	Antibiotics	Cured	CF
2	< 21	IVCM/ PCR	CF	Steroids and antibiotics Antivirals (systemic)	Epithelial defects, ulcerations, corneal ring infiltrates, corneal neovascularization, pain	3	96	Steroids, antibiotics	Cured	20/50
3	< 21	IVCM/ PCR	MM	Steroids and antibiotics. Antivirals (systemic)	Epithelial defects, ulcerations, epithelial infiltrates, corneal ring infiltrates, severe conjunctival inflammation, pain	3	105	Antibiotics, antifungals	Perforation, tectonic keratoplasty[3]	CF
4	>21	IVCM/ PCR	CF	Steroids and antibiotics	Epithelial defects, ulcerations, epithelial infiltrates, corneal ring infiltrates, corneal neovascularization, severe conjunctival inflammation, pain	3	107	Steroids, antibiotics	Cured	20/50
5	<21	IVCM/ PCR	20/50	Steroids and antibiotics	Epithelial defects, ulceration, epithelial infiltrates, corneal neovascularization, pain	2	80	Steroids, antibiotics	Cured	20/50
6	<21	IVCM	20/100	Steroids, antibiotics and PHMB 0.02%. Antivirals (systemic)	Epithelial infiltrates, stromal infiltrates, corneal neovascularization	2	153	None	Cured	20/20
7	>21	IVCM	20/200	Steroids, antibiotics and PHMB 0.02%	Epithelial defects, stromal infiltrates, severe conjunctival inflammation, pain	2	119	None	Cured	20/20
8	<21	IVCM	20/200	Steroids and antibiotics	Epithelial defects, ulceration, pain	2	35	Antibiotics	Cured	20/100
9	>21	IVCM	CF	Steroids, antibiotics, chlorhexidine 0.02%, PHMB 0.02%	Epithelial defects, ulceration, epithelial infiltrates, corneal ring infiltrates, severe conjunctival inflammation, hypopyon	3	119	Antibiotics	Cured	20/200
10	<21	IVCM	20/40	Antibiotics	Epithelial infiltrates, pain	1	66	None	Cured	20/20
11	>21	IVCM	20/40	None	Epithelial infiltrates, pain	1	82	None	Cured	20/20

Stage of disease (Robaei *et al.* 2024).
Stage-1: corneal epitheliopathy only.
Stage-2: at least 1 corneal epithelial defect, perineural or stromal infiltrates, in addition to stage-1 findings.
Stage-3: corneal ring infiltrate and at least one feature of stage-2.
RE = right eye; LE = left eye; IVCM = in vivo confocal microscopy; BCVA = best corrected visual acuity; MM = motu manu; CF = count fingers; PCR = polymerase chain reaction.

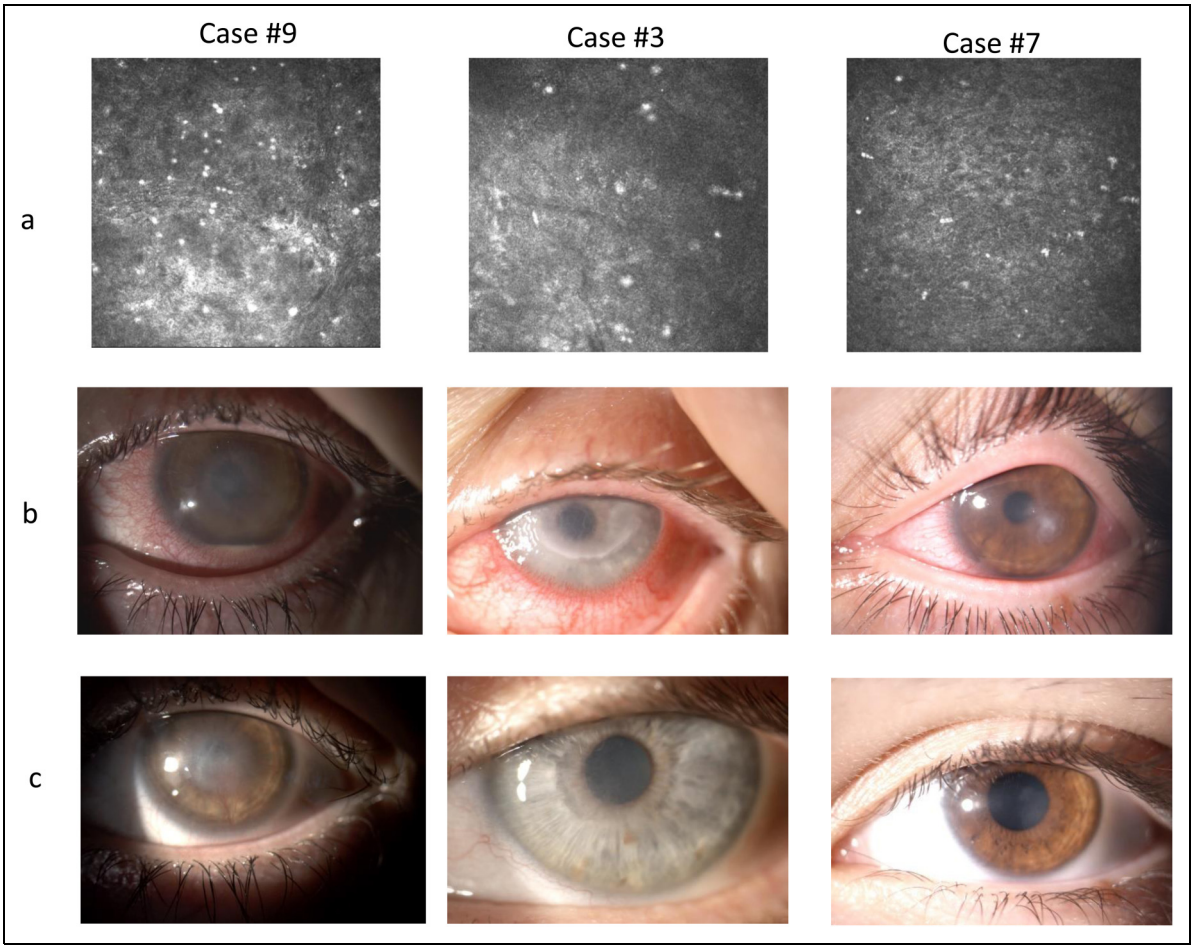

Figure 1. Images of 3 cases of *Acanthamoeba* keratitis treated with PHMB 0.08%. The case number (see Table 1) is shown on the top of each column. Each row includes in vivo confocal microscopy (a), slit lamp image at baseline (b) and slit lamp image at the end of treatment (c). Case #9 (Stage 3 AK). a. Hyper-reflective round elements compatible with *Acanthamoeba* cysts. b. Central stromal infiltrate with hypopyon. c. The cornea infiltrate is less dense and corneal neo vessels from the inferior periphery contribute to resolution of keratitis and inflammation. Case #3 (Stage −3 AK). a. Hyper-reflective round elements compatible with *Acanthamoeba* cysts. b. Ring infiltrate in the inferior corneal sectors, large epithelial defect and severe conjunctival hyperaemia. c. Residual mild subepithelial fibrosis on the left side of the corneal surface which almost reaches the optic zone. Case # 7 (Stage-2 AK). a. Hyper-reflective double-walled round elements compatible with *Acanthamoeba* cysts and cysts in active replication. b. Paracentral stromal infiltrate and epitheliopathy. c. Resolution of stromal infiltrates and residual mild leukoma. Cornea infiltrates disappear and mild leukoma remains evident.

adherence to the therapeutic regimen. It is noteworthy that the medical cure was confirmed after a follow-up of 3 months off-therapy to exclude any late relapse of inflammation or infection.[16] Regarding visual acuity, at presentation 9/12 eyes had a low vision (20/100 or worse) while at the end of treatment 7/12 reached a visual acuity of 20/50 or better. One case with an advanced stage AK required a reconstructive keratoplasty 1 month after starting medical therapy because of peripheral corneal perforation, a common complication in case of AK[21]; this patient was cured after a further course of treatment with PHMB 0.08%, suggesting elimination of *Acanthamoeba* by the combination of PHMB 0.08% and the keratoplasty.

One uncertainty, for many practitioners and patients, which may alter the outcomes elsewhere relates to the possibility that time from the first onset of symptoms to the start of treatment with PHMB 0.08% monotherapy may be further extended than was the case in this study for several reasons as follows. The most common causes of such delays are misdiagnosis, lack of availability of the techniques able to quickly confirm the diagnosis, and the time required to procure an effective anti-amoebic product, which often needs to be imported or compounded. The increase in availability of IVCM and PCR, together with the use of a detailed drug delivery protocol, and the prompt availability of an effective licenced medicinal product can help to achieve a good outcome in patients

with AK. However, it is also important for practitioners to realize that an intensive initial phase and a protracted treatment course are needed to achieve a medical cure. Furthermore, in the event of an inadequate response to treatment additional anti-amoebic drugs, either substituted or in combination, may be required. The development of drug toxicity and worsening infections, even with effective anti-amoebic treatment, may necessitate treatment adjustment or urgent eye surgery to address the infection or restore corneal structure.

We acknowledge the low number of patients included in the present report, as a limitation of the study. However, we thought these initial data of value to substantiate the hypothesis that results obtained in the clinical trial could be replicated in real-world clinical practice, outside a trial setting, providing the drug is delivered and patients monitored as recommended.

Acknowledgments

The authors thank Prof John Dart, Honorary Professor at University College of London and Honorary Consultant at Moorfields Eye Hospital (London), for all comments and suggestions which have strengthened this manuscript.

Contributors

Study design: AF, KAK, AFa, VP. Study implementation (recruiting, assessment, data collection): AF, KAK, EP, AFa, FBe, FBi, EB, PL. Data analysis, manuscript preparation and revision: AF, KAK, EP, AFa, VP. All authors approved the final version of the manuscript, agreed to submit to the current journal, and agreed to be accountable for all aspect of the work.

Data availability statement

All data analysed in the study are included in this article. No additional data are available.

Declaration of conflicting interests

The authors declare that they have no competing interest. Vincenzo Papa is employee of SIFI S.p.A. (manufacturer of PHMB 0.08%).

Ethics approval

The compassionate use program for the use of PHMB 0.08% in patients with *Acanthamoeba* keratitis was approved by the Italian Medicine Agency (AIFA) in 2022. Written informed consent was obtained by all patients before the participation in the program and their treatment was approved by local Ethics Committees.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Vincenzo Papa https://orcid.org/0000-0001-7697-6059

References

1. Zhang Y, Xu X, Wei Z, et al. The global epidemiology and clinical diagnosis of Acanthamoeba keratitis. *J Infect Public Health* 2023 Jun; 16: 841–852.
2. Jasim H, Grzeda M, Foot B, et al. Incidence of Acanthamoeba Keratitis in the United Kingdom in 2015: A Prospective National Survey. *Cornea* 2024 Mar; 43: 269–276.
3. Carnt N, Hoffman JJ, Verma S, et al. Acanthamoeba keratitis: confirmation of the UK outbreak and a prospective case-control study identifying contributing risk factors. *Br J Ophthalmol* 2018 Dec; 102: 1621–1628.
4. Randag AC, van Rooij J, van Goor AT, et al. The rising incidence of Acanthamoeba keratitis: a 7-year nationwide survey and clinical assessment of risk factors and functional outcomes. *PLoS One* 2019 Sep 6; 14: e0222092.
5. Dart JK, Saw VP and Kilvington S. Acanthamoeba keratitis: diagnosis and treatment update 2009. *Am J Ophthalmol* 2009 Oct; 148: 487–499.
6. Oldenburg CE, Acharya NR, Tu EY, et al. Practice patterns and opinions in the treatment of acanthamoeba keratitis. *Cornea* 2011 Dec; 30: 1363–1368.
7. Carrijo-Carvalho LC, Sant'ana VP, Foronda AS, et al. Therapeutic agents and biocides for ocular infections by free-living amoebae of Acanthamoeba genus. *Surv Ophthalmol* 2017 Mar-Apr; 62: 203–218.
8. Kaufman AR and Tu EY. Advances in the management of Acanthamoeba keratitis: a review of the literature and synthesized algorithmic approach. *Ocul Surf* 2022; 25: 26–23.
9. Lim N, Goh D, Bunce C, et al. Comparison of polyhexamethylene biguanide and chlorhexidine as monotherapy agents in the treatment of Acanthamoeba keratitis. *Am J Ophthalmol* 2008 Jan; 145: 130–135.
10. Bagga B, Sharma S, Gour RPS, et al. A randomized masked pilot clinical trial to compare the efficacy of topical 1% voriconazole ophthalmic solution as monotherapy with combination therapy of topical 0.02% polyhexamethylene biguanide and 0.02% chlorhexidine in the treatment of Acanthamoeba keratitis. *Eye (Lond)* 2021 May; 35: 1326–1333.
11. Alkharashi M, Lindsley K, Law HA, et al. Medical interventions for acanthamoeba keratitis. *Cochrane Database Syst Rev* 2015 Feb 24; 2015: CD010792.
12. Papa V, Rama P, Radford C, et al. Acanthamoeba keratitis therapy: time to cure and visual outcome analysis for different antiamoebic therapies in 227 cases. *Br J Ophthalmol* 2020 Apr; 104: 575–581.
13. Scruggs BA, Quist TS, Zimmerman MB, et al. Risk factors, management, and outcomes of *Acanthamoeba* keratitis: a retrospective analysis of 110 cases. *Am J Ophthalmol Case Rep* 2022 Jan 27; 25: 101372.
14. Robaei D, Carnt N, Minassian DC, et al. Therapeutic and optical keratoplasty in the management of Acanthamoeba keratitis: risk factors, outcomes, and summary of the literature. *Ophthalmology* 2015 Jan; 122: 17–24.

15. Di Zazzo A, Varacalli G, De Gregorio C, et al. Therapeutic corneal transplantation in Acanthamoeba keratitis: penetrating versus lamellar keratoplasty. *Cornea* 2022 Mar 1; 41: 396–401.
16. Dart JKG, Papa V, Rama P, et al. The Orphan Drug for Acanthamoeba Keratitis (ODAK) trial: PHMB 0.08% (polihexanide) and placebo versus PHMB 0.02% and propamidine 0.1. *Ophthalmology* 2024 Mar; 131: 277–287.
17. Robaei D, Carnt N, Minassian DC, et al. The impact of topical corticosteroid use before diagnosis on the outcome of Acanthamoeba keratitis. *Ophthalmology* 2014 Jul; 121: 1383–1388.
18. Hoffman JJ, Dart JKG, De SK, et al. Comparison of culture, confocal microscopy and PCR in routine hospital use for microbial keratitis diagnosis. *Eye* 2022; 36: 2172–2178.
19. Wang YE, Tepelus TC, Gui W, et al. Reduction of acanthamoeba cyst density associated with treatment detected by in vivo confocal microscopy in Acanthamoeba keratitis. *Cornea* 2019 Apr; 38: 463–468.
20. Tu EY, Joslin CE, Sugar J, et al. Prognostic factors affecting visual outcome in Acanthamoeba keratitis. *Ophthalmology* 2008 Nov; 115: 1998–2003.
21. Moreira AT and Prajna NV. Acanthamoeba as a cause of peripheral ulcerative keratitis. *Cornea* 2003 Aug; 22: 576–577.