Adv Ther (2009) 26(8):776-783.
DOI 10.1007/s12325-009-0062-1

ORIGINAL RESEARCH

A Combination Povidone-Iodine 0.4%/Dexamethasone 0.1% Ophthalmic Suspension in the Treatment of Adenoviral Conjunctivitis

J. S. Pelletier · K. Stewart · W. Trattler · D. C. Ritterband · S. Braverman · C. M. Samson · B. Liang · J. A. Capriotti

Received: July 6, 2009 / Published online: September 7, 2009 / Printed: September 10, 2009

ABSTRACT

Introduction: The objective of this pilot study was to determine the preliminary efficacy of a novel ophthalmic suspension containing povidone-iodine 0.4% and dexamethasone 0.1% in the treatment of adenoviral conjunctivitis. ***Methods:*** A prospective, open-label, single-armed, phase II clinical trial in humans. Eligible patients with the clinical signs and symptoms of acute conjunctivitis who tested positive for adenoviral antigen by Rapid Pathogen Screening (RPS) Adeno Detector™ were enrolled in a single treatment arm consisting of a combination povidone-iodine 0.4%/dexamethasone 0.1% sterile ophthalmic suspension given four times daily for a minimum of 5 days. RPS Adeno Detector testing was performed at baseline and at each follow-up visit along with ocular fluid sampling by conjunctival swabs. Subsequent analysis performed on all swabs included both adenoviral titer by quantitative polymerase chain reaction (qPCR) and cell culture with confirmatory immunofluorescence (CC-IFA). The primary endpoint was clinical resolution of conjunctival injection and discharge. Secondary measures included reduction of qPCR titers and eradication of infectious virus as determined by CC-IFA. ***Results:*** A total of nine eyes of six patients with clinical signs and symptoms of acute viral conjunctivitis and a positive RPS Adeno Detector test result were enrolled in the study. In eight/nine eyes enrolled in the study, clinical resolution was observed by day 3 or day 4. In six/six eyes with detectable adenovirus by qPCR, significant reduction in viral titer was seen by day 3, day 4, or day 5. In five/six eyes with infectious virus confirmed by CC-IFA at enrollment, elimination of infectivity was achieved by day 4 or day 5. One patient was lost to follow-up. ***Conclusions:*** An ophthalmic suspension

J. S. Pelletier (✉) · K. Stewart · J. A. Capriotti
Ocean Ophthalmology Group, North Miami Beach, Florida, USA. Email: jessepelletier@yahoo.com

W. Trattler
The Center for Excellence in Eye Care, Miami, Florida, USA

D. C. Ritterband · C. M. Samson
New York Eye and Ear Infirmary, New York, New York, USA; New York Medical College, Valhalla, New York, USA

S. Braverman
Braverman Eye Center, Hallandale Beach, Florida, USA

C. M. Sampson · B. Liang · J. A. Capriotti
CLS Pharmaceuticals, New York, New York, USA

containing povidone-iodine 0.4% and dexamethasone 0.1% may be a useful agent in the treatment of acute RPS Adeno Detector-positive conjunctivitis. A further placebo-controlled study with a larger number of patients is warranted.

Keywords: adenovirus; conjunctivitis; cornea; ocular infection; pink eye; povidone-iodine; PVP-I; steroids

INTRODUCTION

External ocular infections caused by adenoviruses are among the most common eye infections seen worldwide. While typically self-limited, they can lead to highly infectious community epidemics, seasonal outbreaks, lost labor productivity, significant patient discomfort, and in some cases permanent visual compromise from long-term immune-mediated sequelae.[1] Although several therapeutic agents have been evaluated for acute viral conjunctivitis in both animal models and human trials, none to date have been approved by the Food and Drug Administration for human conjunctivitis.[2-5] Despite recent interest in the development of anti-viral agents by both industry and academic investigators, there are currently very few clinical trials evaluating anti-adenoviral ocular therapies in humans.[5]

With no effective agents available to treat these common, highly symptomatic, contagious infections, many clinicians adopt idiosyncratic therapeutic regimens that include a mix of comfort measures (ie, artificial tears, cold compresses), topical antibiotics, and in many cases topical steroids. It is widely accepted that a short course of topical corticosteroids (and in some severe cases oral steroids) can limit patient discomfort and prevent some immune-related inflammatory complications of acute viral conjunctivitis. While this strategy may have some efficacy in the short-term amelioration of symptoms, studies in the New Zealand white rabbit model have suggested that even a short course of relatively low-potency corticosteroids without the addition of a suitable anti-viral agent can increase the duration of viral shedding and prolong the infectivity of affected patients.[6] This in turn can potentiate the occurrence of community outbreaks and epidemic transmission in schools, places of business, and medical facilities.

Povidone-iodine (PVP-I) is a commercially available antiseptic with a long history of use in laboratory disinfection, general surgery, and ophthalmology. Dilute PVP-I solutions are toxic to viruses (including human immunodeficiency virus), fungi, parasites, and bacteria.[7,8] Previous studies have demonstrated efficacy in active infections,[9-12] endophthalmitis prophylaxis before[13,14] and after[15] ocular surgery, and in the prevention of neonatal conjunctivitis.[16] Additionally, PVP-I has been described as an effective treatment for acute viral conjunctivitis in a variety of anecdotal reports.[8,9,17] Dexamethasone is a well-tolerated,[18] potent steroid[19] with a long history of use as a topical ophthalmic anti-inflammatory alone and in combination with other agents.[20,21]

It is our intention to investigate a safe, tolerable, efficacious combination agent that includes a powerful anti-viral and a potent topical steroid. In this way, we expect to be able to effectively treat both the inflammatory and infectious components of acute adenoviral conjunctivitis by decreasing the symptomatic period following infection, shortening the duration of viral shedding, and reducing the potential for infectious transmission.

MATERIALS AND METHODS

Study Medication

The combination PVP-I 0.4% (w/w)/dexamethasone 0.1% (w/w) ophthalmic suspension was comprised of PVP-I, dexamethasone, inactive ophthalmic excipients, and sterile water. It was prepared by a licensed compounding pharmacy (Leiter's Pharmacy, San Jose, CA, USA) with extensive experience in ophthalmic drug formulation, produced in a Class 100 ISO-04 sterile facility, clearly labeled, and packaged in appropriate ophthalmic bottles. As reported, the combination of PVP-I and dexamethasone is safe, stable, and comfortable. Additionally, no reaction is seen between dexamethasone and PVP-I when both are stored in the same bottle for up to 18 months.[22]

Study Design

The study was designed as a prospective, open-label, single-armed, descriptive phase II clinical study to evaluate the efficacy of a combination PVP-I 0.4%/dexamethasone 0.1% ophthalmic suspension in the treatment of presumed viral conjunctivitis. The primary goal was to observe the clinical course of antigen-positive Rapid Pathogen Screening (RPS) Adeno Detector™ (Rapid Pathogen Screening; South Williamsport, PA, USA) conjunctivitis treated with PVP-I/dexamethasone while monitoring serial virology markers. It was expected that rapid clinical resolution, or conjunctival injection and discharge scale scores equal to zero, would be accompanied by a decrease in viral titer as treatment progressed. The study was approved by the appropriate institutional review boards and conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent.

Inclusion criteria were the clinical suspicion of acute viral conjunctivitis (conjunctival injection, conjunctival discharge, and symptoms of itching eyes and/or eyelids) with the etiologic agent confirmed by a positive test result for adenoviral antigen with the RPS Adeno Detector test. Exclusion criteria included noninfectious conjunctivitis, a negative RPS Adeno Detector test, pregnancy, age under 3 years, known allergy to any component of the study medication, known steroid-induced glaucoma response, active or history of herpes simplex keratitis, and duration of signs or symptoms for more than 7 days. If both eyes met all inclusion criteria and none of the exclusion criteria, both eyes were enrolled and evaluated separately.

The initial visit included slit-lamp examination and assessment of patient symptoms. Conjunctival injection and discharge were graded by the same investigator, one time per visit on a scale of 0-3 (0=absent, 1=mild, 2=moderate, 3=severe). Conjunctival swabs were obtained using ocular specimen culture kits and were sent immediately for processing to a central virology laboratory (Viracor, Lee's Summit, MO, USA). All swabs sent were analyzed for viral titer by quantitative polymerase chain reaction (qPCR) and viral infectivity by confirmatory immunofluorescence (CC-IFA). Patients were supplied with the study medication and instructed to administer one drop to the affected eye(s) four times per day for a minimum of 5 days. All clinical examinations previous to enrollment and during the study were conducted by an ophthalmologist.

Evaluation and Analysis

Patients were encouraged to return daily for repeat examination and culture. It was not a requirement for patients to complete all 5 days consecutively. In cases where early clinical and

microbiological cure were achieved, patients were still encouraged to continue follow-up until day 5. The scaled scores for conjunctival injection and conjunctival discharge were determined for each subject at each visit. Viral titers and viral infectivity were determined by analysis of conjunctival swab samples by qPCR and CC-IFA for each study subject at each visit. Patient symptoms were elicited at each visit along with any reported discomfort from the administration of the study medication. Moreover, any adverse events noted by the patient or elicited by the treating physician were to be documented and graded. Only descriptive statistics were applied due to the open-label, pilot study design of the current investigation.

Table 1. Results.

Patient A-OD	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
RPS test	+	+	+	–	–		
qPCR titer (DNA copies/mL)	2,100,000	1,700,000	1,200,000	15,700	8400		
CC-IFA	+	+	+	+	–		
Conjunctival injection	3/3	2/3	1/3	0/3	0/3		
Conjunctival discharge	3/3	2/3	0/3	0/3	0/3		
Patient A-OS	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
RPS test	+	+	+	+	–		
qPCR titer (DNA copies/mL)	2,800,000	1,900,000	1,200,000	44,400	100		
CC-IFA	+	+	+	+	–		
Conjunctival injection	3/3	2/3	0/3	0/3	0/3		
Conjunctival discharge	2/3	2/3	0/3	0/3	0/3		
Patient B-OD	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
RPS test	+	+	–	–			
qPCR titer (DNA copies/mL)	1,400,000	2,500,000	12,700	0			
CC-IFA	+	+	+	–			
Conjunctival injection	3/3	1/3	0/3	0/3			
Conjunctival discharge	3/3	0/3	0/3	0/3			
Patient B-OS	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
RPS test	+	+	–	–			
qPCR titer (DNA copies/mL)	3,000,000	1,700,000	21,200	0			
CC-IFA	+	+	+	–			
Conjunctival injection	3/3	1/3	0/3	0/3			
Conjunctival discharge	3/3	0/3	0/3	0/3			

(continued on next page)

Table 1. Results. (*Continued*)

Patient C-OD	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
RPS test	+	–					
qPCR titer (DNA copies/mL)	13,000,000	2,600,000					
CC-IFA	+	+					
Conjunctival injection	3/3	3/3					
Conjunctival discharge	2/3	2/3					
Patient D-OS	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5-7**		**Day 8**
RPS test	+	+		+			+
qPCR titer (DNA copies/mL)	65,000,000	59,000,000		51,000,000			1,100,000
CC-IFA	+	+		+			+
Conjunctival injection	3/3	2/3		0/3			0/3
Conjunctival discharge	3/3	2/3		0/3			0/3
Patient E-OS	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
RPS test	+		–				
qPCR titer (DNA copies/mL)	0		0				
CC-IFA	–		–				
Conjunctival injection	1/3		0/3				
Conjunctival discharge	1/3		0/3				
Patient F-OD	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
RPS test	+	–	–			–	
qPCR titer (DNA copies/mL)	0	0	0			0	
CC-IFA	–	–	–			–	
Conjunctival injection	2/3	1/3	1/3			0/3	
Conjunctival discharge	2/3	0/3	0/3			0/3	
Patient F-OS	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
RPS test	+	–	–			–	
qPCR titer (DNA copies/mL)	0	0	0			0	
CC-IFA	–	–	–			–	
Conjunctival injection	2/3	2/3	1/3			0/3	
Conjunctival discharge	2/3	1/3	0/3			0/3	

Patient C-OD lost to follow-up after day 2.
CC-IFA=confirmatory immunofluorescence; RPS=Rapid Pathogen Screening; qPCR=quantitative polymerase chain reaction.

RESULTS

The results of the study are shown in Table 1. A total of nine eyes of six patients with clinical signs and symptoms of acute viral conjunctivitis and a positive RPS Adeno Detector test result were enrolled in the study. In eight/nine eyes enrolled in the study, clinical resolution was observed by day 3 or day 4. In six/six eyes with detectable adenovirus by qPCR, marked clinical reduction in viral titer was seen by day 3, 4, or 5. In five/six eyes with infectious virus confirmed by CC-IFA at enrollment, elimination of infectivity was achieved by day 4 or day 5.

Patient C demonstrated conjunctival injection and discharge at day 2, but was lost to follow-up thereafter. Eradication of pretreatment infectious virus was achieved no later than day 4 or day 5 except in one case where infectivity persisted at day 8 despite complete clinical resolution. Viral titers determined by qPCR all demonstrated a significant reduction within 5 days. Several patients (E and F) in the current investigation with signs and symptoms of acute conjunctivitis and a positive test result with the RPS Adeno Detector on day 1 (and subsequent days) failed to demonstrate the pretreatment presence of adenovirus by qPCR or by CC-IFA. Patient D maintained qPCR titers and CC-IFA positivity at day 8 despite clinical cure at day 4.

None of the patients enrolled in this study reported any adverse events associated with the medicine.

DISCUSSION

The use of PVP-I as a presurgical disinfectant has been standard in ophthalmology and general surgery for years. Recent interest in PVP-I as a repeated-dose treatment in a variety of infections has contributed to the understanding of more dilute (ie, less than the commercially available 5% or 10%) PVP-I formulations. After encouraging results with this combination in a New Zealand white rabbit model of acute adenovirus infection and acute herpes simplex keratitis (our unpublished, preliminary data), we were led to investigate the use of this dilute PVP-I/dexamethasone formulation in human viral conjunctivitis. We report in the current investigation systematic human investigation of a combination PVP-I/steroid combination for the treatment of both the inflammatory and infectious components of acute adenoviral conjunctivitis. While corticosteroids alone have been shown in the adenovirus 5 New Zealand white rabbit model to increase the duration of viral shedding and the absolute viral titer,[6] this trend was not noted in our previous New Zealand white rabbit study or in this human pilot study. We observed rapid resolution of conjunctival injection and discharge in all eyes with coincident decrease in viral titers (where present in the pretreatment analysis). Classically, the duration and intensity of ocular inflammatory findings in acute adenoviral conjunctivitis are variable. In some untreated infections, early conjunctival inflammation may be severe and persist for weeks with gradual improvement.[23,24] Keratitis often complicates more severe cases, and may appear early or late in the infectious period. In contrast, milder forms of the disease are also known and can range from shorter courses with milder symptoms of injection and discharge. It is likely that a number of subclinical infections can also be encountered, though these would naturally be expected to self-resolve. Adenoviral conjunctivitis may also be an underappreciated cause of recurrent, chronic conjunctivitis and keratitis lasting months to years.[23,24]

Limitations of the study where pretreatment presence of adenovirus by qPCR or by CC-IFA

was not confirmed may include false-positive RPS Adeno Detector test result, poor culturing technique, or false-negative CC-IFA and qPCR testing. In these cases, the infectious etiology may have been viral other than adenovirus or bacterial. We cannot, within the current limited study, rule out possible allergic or noninfectious causes. It is of note, however, that these patients also achieved rapid clinical resolution.

This investigation was neither substantially powered nor designed to allow statistically significant comparison to a placebo, conventional symptomatic therapy (tears, compresses, etc.) or non-intervention. Also, patient compliance to the study medication regimen could not be ensured. Currently, there is no literature documenting trends of qPCR titers in cases of untreated adenoviral conjunctivitis. It is possible that the values obtained in this study are similar to those that would be obtained in placebo-treated eyes. Conversely, it is plausible that untreated or placebo-treated patients' adenoviral qPCR titers are significantly more robust than what was documented in this pilot study. This may explain Patient D-OS positive qPCR titer at day 8. Despite the limitations of the design, though, it appears that the combination of 0.4% PVP-I/0.1% dexamethasone may have utility in the treatment of acute adenoviral conjunctivitis as determined by analysis of both clinical and microbiological endpoints.

The potential of a steroid/antiseptic combination that is comfortable for the eye and efficacious against acute viral conjunctivitis cannot be overstated. While the hazards of ocular corticosteroid are well documented, we believe the inhibition of immune-related phenomena during the course of acute adenoviral conjunctivitis to be of great importance. The possibility of rapid clinical and/or microbiological cure makes it unlikely that steroid-related side effects will manifest. In addition, the broad spectrum and absence of any known microbial resistance to PVP-I may have utility in steroid-containing preparations for a variety of viral, bacterial, and fungal infections of the ocular surface.

CONCLUSION

This pilot study demonstrates successful human use of a combination PVP-I/dexamethasone preparation in the setting of acute conjunctivitis, confirmed by an RPS Adeno Detector test. It will be the subject of future placebo-controlled phase II/III trials to further quantify the treatment effect in acute adenoviral conjunctivitis and evaluate the therapeutic benefit of a PVP-I/dexamethasone combination in other infections of the ocular surface.

ACKNOWLEDGMENTS

This investigation was supported by an unrestricted research grant from Foresight Biotherapeutics, Inc., New York, USA.

REFERENCES

1. Ford E, Nelson KE, Warren D. Epidemiology of epidemic keratoconjunctivitis. Epidemiol Rev. 1987;9:244-261.

2. Hillenkamp J, Reinhard T, Ross R, et al. The effects of cidofovir 1% with and without cyclosporin A 1% as a topical treatment of acute adenoviral keratoconjunctivitis: a controlled clinical pilot study. Ophthalmology. 2002;109:845-850.

3. Teuchner B, Nagl M, Schidlbauer A, et al. Tolerability and efficacy of N-chlorotaurine in epidemic keratoconjunctivitis – a double-blind, randomized, phase-2 clinical trial. J Ocul Pharmacol Ther. 2005;21:157-164.

4. Romanowski EG, Gordon YJ. Efficacy of topical cidofovir on multiple adenoviral serotypes in the New Zealand rabbit ocular model. Invest Ophthalmol Vis Sci. 2000;41:460-463.

5. Clinicaltrials.gov web site. An evaluation of the efficacy and safety of AL-46383A ophthalmic solu-

tion for the treatment of adenoviral conjunctivitis. Identifier: NCT00901693. Available at: http://clinicaltrials.gov/ct2/results?term=NCT00901693. Accessed August 2009.

6. Romanowski EG, Roba LA, Wiley L, Araullo-Cruz T, Gordon YJ. The effects of corticosteroids on adenoviral replication. Arch Ophthalmol. 1996;114:581-585.

7. Bhagwat D, Oshlack B. Stabilized PVP-I solutions. United States Patent 5126127. June 30, 1992. Available at: www.freepatentsonline.com/5126127.html.

8. Berkelman R, Holland B, Anderson R. Increased bactericidal activity of dilute preparations of povidone-iodine solutions. J Clin Microbiol. 1982;15:635-639.

9. Hale E. The treatment of corneal ulcer with povidone-iodine (Betadine). N C Med J. 1969;30:54-56.

10. Isenberg SJ, Apt L, Valenton M, et al. A controlled trial of povidone-iodine to treat infectious conjunctivitis in children. Am J Ophthalmol. 2002;134:681-688.

11. Schuhman G, Vidic B. Clinical experience with povidone-iodine eyedrops in conjunctivitis and keratoconjunctivitis. J Hosp Infect. 1985;6(suppl. A): 173-175.

12. Pernicky J. Our experience with the use of povidone-iodine drops in the treatment of viral conjunctivitis [article in Czech]. Czechoslovenska Oftalmologie. 1994;50:323-325.

13. Apt L, Isenberg SJ, Yoshimori R, Spierer A. Outpatient topical use of povidone-iodine in preparing the eye for surgery. Ophthalmology. 1989;96:289-292.

14. Speaker MG, Menikoff JA. Prophylaxis of endophthalmitis with topical povidone-iodine. Ophthalmology. 1991;98:1769-1775.

15. Isenberg SJ, Apt L, Yoshimori R, Pham CB, Lam NK. Efficacy of topical povidone-iodine during the first week after ophthalmic surgery. Am J Ophthalmol. 1997;124:31-35.

16. Isenberg SJ, Apt L, Wood M. A controlled trial of povidone-iodine as prophylaxis against ophthalmia neonatorum. N Engl J Med. 1995;332:562-566.

17. Abel R, Abel AD. Use of povidone-iodine in the treatment of presumptive adenoviral conjunctivitis. Ann Ophthalmol. 1998;30:341-343.

18. Weijtens O, Schoemaker R, Romijn F, et al. Intraocular penetration and systemic absorption after topical application of dexamethasone disodium phosphate. Ophthalmology. 2002;109:1187-1191.

19. Awan M, Agarwal P, Watson D, et al. Penetration of topical and subconjunctival corticosteroids in human aqueous humor and its therapeutic significance. Br J Ophthalmol. 2009;93:708-713.

20. Holland EJ, Bartlett JD, Paterno MR, et al. Effects on loteprednol/tobramycin versus dexamethasone/tobramycin on intraocular pressure in healthy volunteers. Cornea. 2008;27:50-55.

21. Mohan N, Gupta V, Tandon R, et al. Topical ciprofloxacin-dexamethasone combination therapy after cataract surgery randomized controlled clinical trial. J Cataract Refract Surg. 2001;27:1975-1978.

22. Samson CM, Capriotti JA, Liang B. Ophthalmic compositions comprising povidone-iodine. United States Patent Application 20070219170. September 20, 2007. Available at: www.freepatentsonline.com/y2007/0219170.html.

23. Krachmer J, Mannis M, Holland E. Cornea and External Disease: Clinical Diagnosis and Management. St. Louis: Mosby; 1997:773-775.

24. Smolin G, Thoft R. The Cornea: Scientific Foundations and Clinical Practice. Fourth Edition. New York: Lippincott Williams & Wilkins; 2004:359-364.