Reducing Adenoviral Patient Infected Days (RAPID) Study: Design and Baseline Characteristics

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Introduction

Adenoviral conjunctivitis (Ad-Cs), also known as "pink eye", is a prevalent condition that is highly contagious.[1,2] The morbidity associated with this infection has considerable economic impact on society. An estimated $670 million is spent annually on the management of acute conjunctivitis, and afflicted patients miss on average five days of work or school.[3] As one recent high-profile example, the prolonged work absence of Bob Costas during the 2014 Sochi Olympics illustrated the potential impact of this condition.

Photo Credit: NBC

There are currently no FDA-approved treatments for Ad-Cs. Povidone iodine (Betadine) is inexpensive, has broad-spectrum antimicrobial effectiveness and has an excellent safety profile.[4] Off-label use of Betadine to treat Ad-Cs has been promoted by influential editorials and reviews within the optometric and ophthalmological communities, and our previous survey data indicates that a significant proportion of clinicians have treated Ad-Cs with Betadine (Figure 1).[5] Unfortunately, previous studies of Betadine for the treatment of Ad-Cs have been uncontrolled, unmasked and/or underpowered.

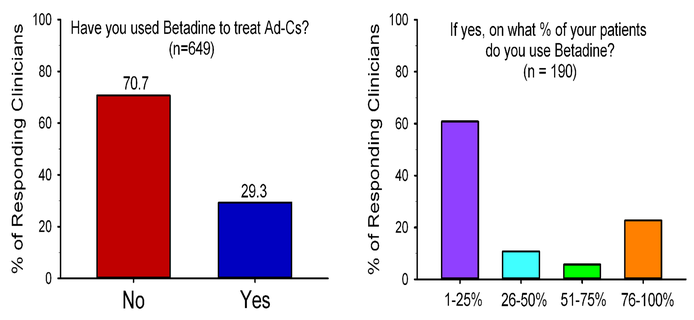

Figure 1. A) Survey of 649 optometrists and ophthalmologists that attended 7 clinical conferences in 2013 revealed that over a quarter had used Betadine in the past to treat Ad-Cs. **B)** Of those that responded 'yes', the % of Ad-Cs patients that they reported using Betadine to treat the condition.

Our goal is to conduct a doubled-masked randomized clinical trial that evaluates whether an in-office application of 5% Betadine is more effective than artificial tears at reducing viral load and improving symptoms in patients with Ad-Cs. The RAPID (Reducing Adenoviral Patient-Infected Days) Study is a 2-year planning study to estimate key parameters that will aid the design of such a randomized trial.

Here, we present baseline characteristics (signs and symptoms) for subjects that were screened for enrollment during the first 15 weeks of recruitment for the RAPID Study.

RAPID Study Design

Patients that are ≥ 18 years old and presenting with a red eye with symptom onset ≤ 4 days are screened for eligibility.

Screened patients are clinically examined and administered symptom survey (Table 1).

To be eligible for treatment randomization, patients must test positive on the AdenoPlus adenovirus immunoassay test (Rapid Pathogen Screening, Inc., Sarasota FL), must not be pregnant, and must not have a thyroid condition or iodine allergy.

Eligible patients are randomized to an in-office lavage of artificial tears or 5% Betadine solution. Both groups are given single-use preservative-free artificial tears for home use (q.i.d.).

Procedure	Screening Exam Pts. ≥ 18 yrs. presenting w red eye	Follow-up Exams Randomized Pts. at 1-2, 4-5, 7, 14, 21 days
	Unmasked or Masked Clinician/Technician	Masked Clinician or Masked Technician
Written Informed Consent	X	n/a
Examiner-Administered Symptom Survey	X	X
Medical and Ocular History	X	X
Snellen Visual Acuity (Pinhole if VA worse than 20/20)	X	X
Lymph Node Palpation	X	X
Slit Lamp Examination, Grading of Ocular Signs and Fluorescein Staining	X	X
Clinician Prediction of Pink Eye Etiology	X	n/a
AdenoPlus Testing and Photograph of Test Display	X	Continue RPS testing until 2 negative results
Swab for qPCR Analysis Inferior nasal conjunctiva	X	X
Randomization to artificial tears or 5% PVP-I (Betadine 5%)	Randomized treatment by unmasked examiner	n/a
Pt. receives artificial tears	X	X

Table 1. Summary of procedures at baseline and follow-up visits. Procedures in unshaded boxes are performed on all screened subjects; those in shaded boxes are performed on eligible subjects with an AdenoPlus-positive test that are randomized to treatment. Subjects and examiners for follow-up visits are masked to treatment.

Results

- Over the first 15 weeks, 17 patients that were ≥ 18 years old (42.9 + 14.4 years; 70.6% female), and presenting with a red eye of ≤ 4 days onset, were screened for the study.
- Of the 17 patients, 10 tested positive using the AdenoPlus immunoassay test.
- The patient-reported symptom survey scores (Figure 2) and the examiner-graded clinical signs (Figure 3) for the AdenoPlus-negative (n = 7) and AdenoPlus-positive (n = 10) patient groups were tabulated and compared.
- The mean scores for patient-reported symptoms and examiner-graded signs trended higher in the AdenoPlus-positive patients, but only the clinical grading of follicular and papillary responses was statistically higher, as compared to the AdenoPlus-negative subjects, in this initial sample or early enrollees.

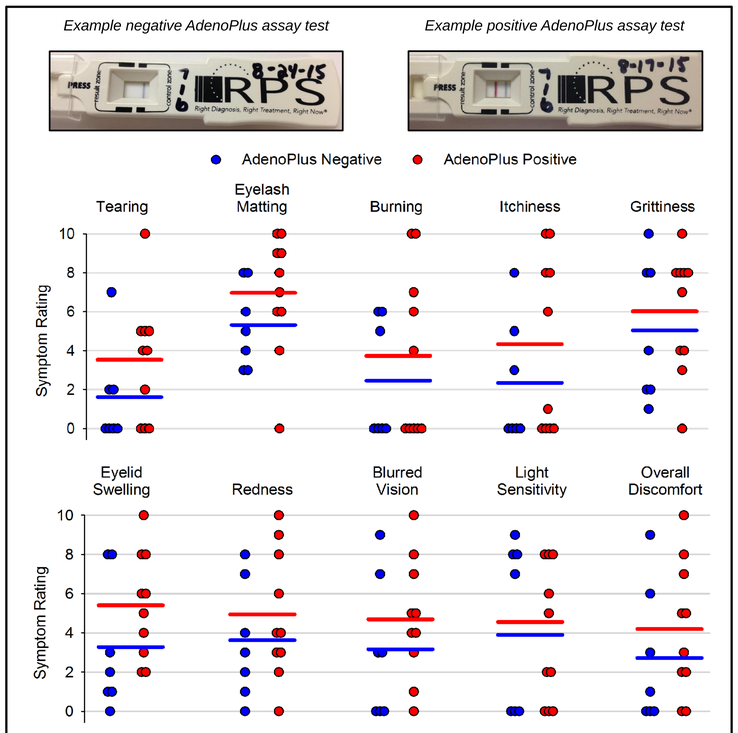

Figure 2. Dot density plots showing the severity of symptoms, reported on a scale from 0 (not at all bothersome) to 10 (very bothersome), in subjects that tested negative (n = 7; blue circles) and positive (n = 10; red circles) using the RPS AdenoPlus immunoassay test. Horizontal lines represent mean values for symptom ratings in AdenoPlus-negative (blue) and -positive (red) subjects. No scores were statistically different (p > 0.05, Mann-Whitney test) between the two subject groups.

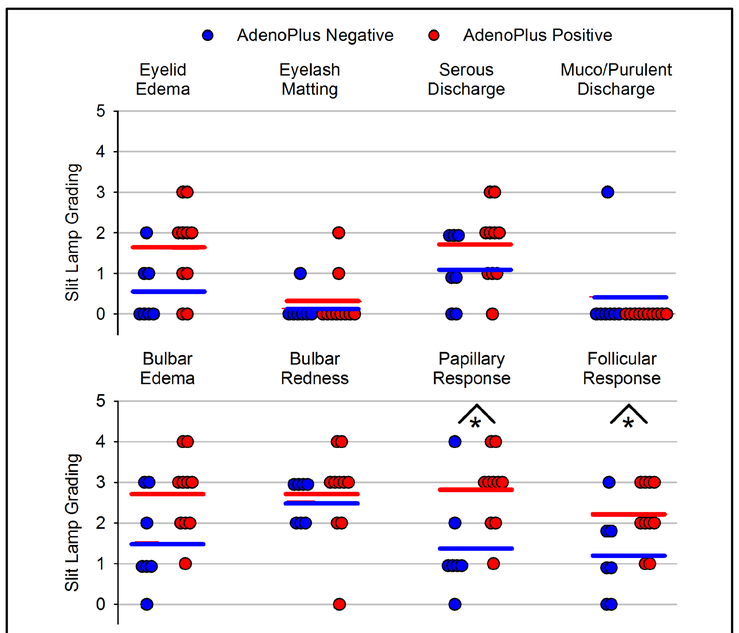

Figure 3. Dot density plots showing the frequency of graded signs, reported on a scale from 0 (absent) to 4 (severe), observed during slit lamp examination by clinician on AdenoPlus-negative (n = 7; blue circles) and -positive (n = 10; red circles) subjects. Horizontal lines represent mean values for clinical sign grades in the two subject groups. The papillary (p = 0.028) and follicular (p = 0.032) responses were significantly higher (Mann-Whitney test) in the RPS-positive subjects.

Results

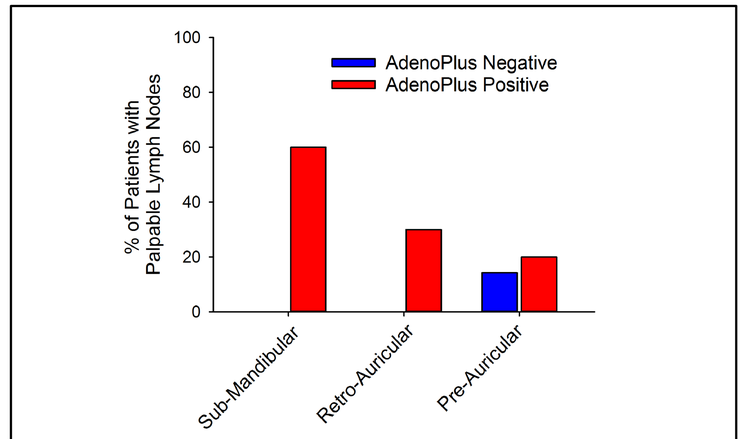

Figure 4. Percentage of AdenoPlus-negative (n = 7; blue bars) and AdenoPlus-positive (n = 10; red bars) subjects that had palpable lymph nodes (sub-mandibular, retro-auricular, pre-auricular).

- 60% of the AdenoPlus-positive patients had at least one palpable lymph node (sub-mandibular, retro-auricular or pre-auricular), as compared to 14% of the AdenoPlus-negative subjects (Figure 4).
- Of the 10 AdenoPlus-positive subjects, 9 were randomized to treatment (either Betadine or artificial tears lavages). One subject was excluded from treatment randomization due to a thyroid condition.
- All 9 subjects that were randomized to treatment completed 21 days of follow-up. Analysis of the data from follow-up visits (post-treatment randomization) will not be performed until study recruitment has closed.

Conclusions

- This work describes the RAPID study design and baseline characteristics (graded signs and symptoms) of the red eye patients that were screened early in the study.
- The initial data indicates Ad-Cs is a condition associated with significant clinical signs as well as highly bothersome patient-reported symptoms.
- Of patients presenting with a red eye that were screened for the study, 58.8% tested positive using the AdenoPlus immunoassay test.
- A high retention rate (100%) during the 21 days of follow-up was observed in this cohort of early patient enrollees, supporting the feasibility of a larger-scale clinical trial.

References

1. Sheldrick JH, Wilson AD, Vernon SA, Sheldrick CM. Management of ophthalmic disease in general practice. British Journal of General Practice, 1993; 43(376):459-62. PubMed PMID: 8292417.
2. McDonnell PJ. How do general practitioners manage eye disease in the community? British Journal of Ophthalmology, 1988; 72(10):733-6. PubMed PMID: 3191073.
3. Udeh BL, Schneider JE, Ohsfeldt RL. Cost effectiveness of a point-of-care test for adenoviral conjunctivitis. American Journal of the Medical Sciences, 2008; 336(3):254-64. PubMed PMID: 18794621.
4. Isenberg SJ, Apt L, Campeas D. Ocular applications of povidone-iodine. Dermatology. 2002; 204 Suppl 1:92-5. PubMed PMID: 12011529.
5. Than T, Hartwick A, Shorter E, Johnson S, Lonsberry B, Gordon M, Freddo T. How to manage adenoviral conjunctivitis. Optometry Times, Feb 18 2004. (Online: http://optometrytimes.modernmedicine.com/optometrytimes/news/how-manage-adenoviral-conjunctivitis)

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Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT02472223