ORIGINAL RESEARCH

Topical Tacrolimus (0.1%) As A Treatment Modality for Adenoviral Corneal Sub-epithelial Infiltrates

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ABSTRACT

Introduction: Epidemic Kerato-conjunctivitis (EKC), an ocular disease involving cornea is caused by adenoviruses. Present study was undertaken to assess efficacy and safety of topical 0.1% Tacrolimus in the treatment of adenoviral sub-epithelial infiltrates (SEI).

Material and Methods: This prospective non-controlled interventional case study included 40 patients (67 eyes) with SEIs following adenoviral conjunctivitis .0.1% Tacrolimus gel was used twice daily after appearance of grade 3-5 SEIs as primary treatment alone for a duration of 12 weeks and were followed up for 40 weeks. Patients were instructed to instill a rice-grain size amount of tacrolimus gel in the lower fornix twice a day. The recorded data included age, sex, best corrected visual acuity (BCVA), intraocular pressure (IOP), biomicroscopy findings, and duration of therapy.

Results: Our study group consisted of 23 (57.5%) males and 17 (42.5%) females. Mean age of 37.2 ± 18.3 years was noted. Patients were treated for a period of 12 weeks and the average follow up time of the patients was 40 ± 5.3 weeks. The mean BCVA (logarithm of the minimum angle of resolution) before and after the treatment were 0.21±0.13 and 0.06±0.07 respectively (p=0.003). There was complete resolution if SEIs in 60 eyes (89.55%) , 4 eyes (5.9%) ended up with clear central cornea with peripheral scarring , 3 eyes (4.4%) continued to have SEIs. 16 patients complained of burning sensation for first few days after application of tacrolimus gel but none of them reported intolerance to warrant discontinuation of the drug. No serious side effects were noted during the treatment and follow-up period.

Conclusion: Topical 0.1 % tacrolimus seemed to be an effective corticosteroid-sparing agent for the treatment of SEIs after adenoviral conjunctivitis.

Keywords: Epidemic Keratoconjunctivitis, Corneal subepithelial infiltrates, Topical 0.1% tacrolimus

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INTRODUCTION

Epidemic kerato-conjunctivitis (EKC) is the severest ocular disease caused by adenoviruses.[1] Adenovirus 8, 19, and 37 are the serotypes most commonly associated with EKC.[2] The clinical picture Adenovirus 8 is the prototype of ocular changes induced by adenoviral disease. Corneal involvement can be detected as early as two days after the onset of the disease or progression to sub-epithelial infiltrates (SEIs) in 43% of patients.[3,4] SEIs most commonly diminish with time; however, even with treatment, SEIs may cause photophobia and blurred vision for many months and, in some cases, may lead to visually significant scarring. Tacrolimus (FK-506) is an immunosuppressive drug used mainly after organ transplant to lower the risk of organ rejection. It has similar immunosuppressive properties to cyclosporin, but is much more potent. Immunosuppression with tacrolimus is associated with a significantly lower rate of acute rejection compared with ciclosporin-based immunosuppression.[5] Off lately topical Tacrolimus (0.03%) has been used for the treatment of SEIs.[6] We evaluate the efficacy of topical 0.1% tacrolimus for the treatment of SEIs.

MATERIAL AND METHODS

This prospective non-controlled interventional case study was carried out in the department of Cornea and Refractive Services at Aravind Eye Hospital, Coimbatore from June 2013 to December 2014 and included 40 patients (67 eyes) with SEIs following adenoviral conjunctivitis .0.1% Tacrolimus gel was used twice daily after appearance of grade 3-5 SEIs (Table 1) as primary treatment alone for a duration of 12 weeks and were followed up for 40 weeks. Patients were instructed to instill a rice-grain size amount of tacrolimus gel in the lower fornix twice a day. The recorded data included age, sex, best corrected visual acuity (BCVA), intraocular pressure (IOP), biomicroscopy findings, and duration of therapy. The treatment was considered successful if there was a resolution in SEIs, as well as BCVA stabilization or improvement. The treatment was considered unsuccessful if the patient could not tolerate tacrolimus or if there was an increase in SEIs.

Statistical analysis

All analysis were carried out using Statistical Package for Social Sciences software. Wilcoxon signed rank test was used for statistical analysis and values of $p < 0.05$ were considered to be significant.

RESULTS

Our study group consisted of 40 patients with involvement in 67 eyes, of which 23 (57.5%) were males and 17 (42.5%) were females. Mean age of 37.2 ± 18.3 years was noted. Patients were treated for a period of 12 weeks and the average follow up time of the patients was 40 ± 5.3 weeks. The mean BCVA (logarithm of the minimum angle of resolution) before and after the treatment were 0.21 ± 0.13 and 0.06 ± 0.07 respectively (p=0.003). There was complete resolution if SEIs in 60 eyes (89.55%), 4 eyes (5.9%) ended up with clear central cornea with peripheral scarring, 3 eyes (4.4%) continued to have SEIs. All the patients had decrease in symptoms such as glare, photophobia , tearing and foreign body sensation. 16 patients complained of burning sensation for first few days after application of tacrolimus gel but none of them reported intolerance to warrant discontinuation of the drug. No serious side effects were noted during the treatment and follow-up period. Overall, patients noted an improvement in vision and satisfaction with topical 0.1% tacrolimus treatment.

DISCUSSION

Adenoviral keratoconjunctivitis can present with symptoms such as chemosis, eye pain, tearing, hyperemia, photophobia and swelling of eyelids. Approximately 80% of the patients develop keratitis with SEIs.[7,8] SEIs can result in a decrease of visual acuity, glare,foreign body sensation , irregular astigmatism and photophobia. Studies report decrease in visual acuity caused by SEI which can resolve in a matter of weeks or persist for years in some cases.[7,9] Various treatment modalities such as trifluridine, vidarabine and ganciclovir have been tried but none were found to be effective in treatment.[10,11] Long term corticosteroid use in adenovirus infections are effective but can cause cataracts, glaucoma and super infections.[12] In 1989, Kobayashi first reported that tacrolimus suppressed corneal graft rejection in rabbits. Since then, the use of tacrolimus is of special interest in ophthalmology because it is indicated to be effective in the treatment of immune-mediated diseases such as corneal graft rejection, ocular inflammation, ocular pemphigoid, and uveitis.[13] Topical tacrolimus in a strength of 0.03% has been used by investigators successfully in adenoviral keratoconjunctivitis.[6,14] We evaluated the efficacy of 0.1% topical tacrolimus for treatment of adenoviral SEIs.

Treatment with 0.1% tacrolimus resulted in resolution of SEIs in 64 eyes, (95.6%). This figure is better than that reported by Ghanem et al and Levinger et al by using 0.03% of the same drug.[6,14] It also betters results obtained by Okumus et al, who used 0.05% topical cyclosporine for the same. [15] All of the above mentioned eyes had an improved mean BCVA (logarithm of the minimum angle of resolution) before and after the treatment; 0.21 ± 0.13 and 0.06 ± 0.07 respectively. We treated all the patients for a shorter time period (12 weeks) as compared to Ghanem et al (8.8 ± 2.4 months) and Levinger et al (22 weeks) which proves 0.1% tacrolimus a more potent option for treating adenoviral SEIs, requiring shorter treatment periods. All the patients who received the treatment had subjective improvement in symptoms like glare, photophobia, foreign body sensation irrespective of the clinical outcome. Apart for burning sensation for first few days of usage reported by 16 patients, no serious side –effects were noted to warrant cessation of treatment. One study conducted by Freeman et al on safety and efficacy of topical 0.1% tacrolimus for atopic dermatitis of eyelids showed no side effects treated for 8 weeks and followed up for additional 2 weeks.[16]

Grade	Features
0	Poorly staining , minute punctate opacities within the corneal epithelium
1	Fine punctate epithelial keratitis (PEK)
2	Fine and coarse PEK. Stains brightly with rose Bengal
3	Coarse granular infiltrates within deep epithelium, early sub epithelial infiltrates, diminished PEK
4	Classic sub epithelial infiltrates without PEK
5	Punctate epithelial granularity adjacent to and distinct from the sub epithelial infiltrates

Table-1: Grading of sub-epithelial infiltrates (SEI) based on corneal involvement

CONCLUSION

We used tacrolimus alone, without any additional use of steroids and found it to be more potent in higher concentrations (0.1%) and a safe alternative to steroids and causing a considerable reduction in ocular morbidity caused by adenoviral SEIs. Having an excellent safety profile, we recommend use of topical 0.1% tacrolimus gel in all cases of severe SEIs, however more studies with longer follow-up are required to support our study.

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