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Development Of An Animal Model For Ocular Adenoviral Infection
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Ocular adenoviral infections occur in epidemics worldwide, and are associated with significant patient morbidity. At the present time, there is no animal model in which to evaluate new antivirals or to study the pathogenesis of ocular adenoviral infection. Following ocular inoculation of NZ rabbits with different adenoviral serotypes, clinical signs of conjunctivitis, keratitis, and iritis were evaluated for 30 days. Replicating virus on the ocular surface was determined by serial ocular titers. Preliminary studies in 44 NZ rabbits suggested differences in adenoviral pathogenicity based on serotype: Ad5 > Ad8 >> Ad19. Our most successful ocular model to date was developed in 32 NZ rabbits infected with a clinical isolate of Ad5. Using a paired-eye design, reproducible acute ocular infection was demonstrated in 32/32 infected eyes (100%), with mean viral replication for 8.3 days ($P < .0001$). Peak ocular viral titers (10^3 pfu/ml) were achieved on Day 3 p.i. and represented a 2 log increase (100x) over day 1 p.i. Ocular viral replication was associated with acute conjunctivitis (24/34 eyes, 75%), and delayed onset presumed immune-mediated clinical disease: blepharoconjunctivitis (21/32 eyes, 66%), iritis (29/32 eyes, 91%), corneal edema 32/32 eyes, 100%), and subepithelial corneal infiltrates (30/32 eyes, 94%). We conclude that a useful animal model of adenoviral ocular infection is available, and preliminary results with antiviral therapy will be presented.

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An Antisense Oligonucleotide to the HSV-1 UL-13 Gene is Effective Against Herpetic Keratitis.
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Antisense oligonucleotides are active against several viruses in cell culture. Little is known, however, about the effectiveness of antisense oligos in animal models of viral infection. Animal models of HSV induced keratitis are well suited for such studies. The drugs can be applied topically in aqueous solution and several parameters of the infection can be monitored. Using a murine model we have tested the effectiveness of a phosphorothioate antisense-oligo directed against the UL-13 gene of HSV-1 (ISIS-1082, GCCGAGGTCCATGTCGTACGC) in treating herpetic keratitis. Four to five week old female BALB/c mice were infected with $1x10^5$ pfu of HSV-1 KOS following scratching of the cornea. Treatment was begun 4 hr post-infection (pi) and was carried out by placing a 10 μl drop of the drug on the cornea and holding the eye open for 15 sec. Treatments were given every 2 hr for 16 hr/day during the first 7 days and every 4 hr for 16 hr/day during days 8-14. Treatment groups (10 mice/group) included buffer only (50 mM sodium acetate, pH 5.8; 0.15 M NaCl), ISIS-1082 (0.1%, 0.3%, 1.0%), and HSV-1 KOS only. Treatment with ISIS-1082 did not affect the severity of blepharitis but mice treated with 0.3% and 1.0% ISIS-1082 healed slightly faster ($p<0.05$). Treatment with 0.3% and 1.0% ISIS-1082 also reduced stromal disease and vascularization on days 11, 13, and 15 pi. The reduction in disease was significant ($p<0.05$) on some days but not others, probably because of small sample size and variability in the disease. More animals are currently being tested. Dose response effects were seen at 0.1% and 0.3% ISIS-1082 but 1.0% ISIS-1082 was no better than the 0.3% solution. The doses causing a 50% reduction in disease scores (DS_{50}) on day 15 pi were 0.17%, 0.25%, and 0.22% for blepharitis, vascularization, and stromal disease respectively. Treatment with ISIS-1082 affected neither viral titers in the eyelids, eyes, or trigeminal ganglia, nor establishment of reactivatable latent infections. The significant reduction in ocular disease severity seen with the 0.3% and 1.0% ISIS-1082 solutions is encouraging and suggests that antisense oligos may be useful in treating HSV keratitis.