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Recent advances in ophthalmic therapy

Ron Ofri DVM, PhD, DECVO
Koret School of Veterinary Medicine, Hebrew University of Jerusalem, PO Box 12, Rehovot 76100, Israel

Treatment of canine keratoconjunctivitis sicca

Keratoconjunctivitis sicca (KCS) is a progressive inflammation of the cornea and conjunctiva caused by a deficiency in the aqueous component of the tear film. Historical treatment of the disease included artificial tears, mucolytic agents, antibiotics (in cases of infection/ulceration) and pilocarpine, a parasympathomimetic agent which would stimulate cholinergic innervation of the lacrimal gland.

In 1989, treatment of canine KCS was revolutionized when Kaswan et al reported that topical cyclosporine (CsA) is an efficacious drug in the treatment of the disease. Most cases of canine KCS are probably caused by an autoimmune inflammation of the tear gland, and it is believed that CsA exerts a therapeutic effect by inhibiting T-helper lymphocyte proliferation and infiltration of lacrimal gland acini, allowing for regeneration of the gland and the return of secretory function.

Even though CsA has become the treatment of choice for canine KCS, it is not 100% effective. It has been reported that the drug, administered topically as a 0.2% ointment and as a 1% or 2% oil-based solution, improved tear production in 71-86% of dogs with KCS. Therefore, there is a need to find new drugs, which can be used to treat dogs that do not respond to CsA treatment, or dogs that suffer adverse effects (topical irritation, etc.).

Two related drugs that may be promising alternatives to CsA are pimecrolimus and tacrolimus. Unlike CsA, which is an immunosuppressive drug, these are considered immunomodulating drugs. They are ascomycin-derived macrolides that bind specifically to the cytosolic receptor, immunophilin macrophilin-12. The resulting drug-receptor complex inhibits calcineurin-dependent dephosporylation-activation of specific nuclear factors in activated T cells, thus preventing transcription of pro-inflammatory cytokines. This results in lack of activation of T helper cells types 1 and 2. T cell proliferation and mast cell activation are also inhibited. It is hypothesized therefore that these drugs could reduce cell-mediated inflammation of the lacrimal gland.

Two studies will be presented. The first shows that pimecrolimus is just as effective as cyclosporine in improving tear production, and more effective in reducing clinical signs of KCS. The second study shows that tacrolimus improves tear production in dogs that are resistant to cyclosporine therapy. Therefore, these drugs are a promising alternative to topical CsA for treatment of KCS and may be beneficial in patients with less than optimal response to topical CsA.

Treatment of melting corneal ulcers: inhibiting matrix metalloproteinases

Uncomplicated corneal abrasions (superficial damage to epithelium) or ulcers (deeper damage, involving corneal stroma) will heal uneventfully, though topical antibiotic treatment is usually provided, to avoid infection. However, due to microbial infection or to extensive stromal involvement, some corneal ulcers undergo 'melting'. This process, also known as keratomalacia, is characterized by rapid and progressive degeneration of the corneal stroma, which may result in corneal perforation within 24 hours. This rapid degradation of corneal stroma is the result of proteinase activity. These enzymes, also known matrix metalloproteinases (MMP's) are secreted by the infective micro-organisms (e.g., Pseudomonas), but are also found in the tear film, white blood cells and corneal cells. The body's own MMP's play an important role in normal corneal repair and healing, but an increase in their levels or activity will cause degradation of the corneal collagen, elastin, etc.

Several drugs and substances have recently been shown to have an inhibitory effect on MMP activity. The effect is usually mediated by chelating co-factors, such as zinc or calcium, required for MMP activity. The resulting inhibition rate of MMP activity is usually > 90%. Therefore, these drugs could become important therapeutic agents in the treatment of ulcerative keratitis and keratomalacia. The drugs include:

1. N-acetyl cysteine - applied as a 10%-20% topical solution every 1-4 hours.
2. Tetracycline - may be administered topically (0.025-0.1%) or systemically. The anti-MMP activity is in addition to the drug's antimicrobial effect.
3. EDTA - topical treatment with 0.05-0.2% solution
4. Autogenous serum - about 10% of the proteins in the serum are α2-macro globulins, which are potent MMP inhibitors. Serum is obtained from blood, following clotting and centrifugation, and can be applied every 1-2 hours. It should be replaced every 8 days (to avoid contamination). Growth factors in the serum may also promote corneal healing.

Treatment of feline herpes keratoconjunctivitis

Treatment of feline herpes virus is very frustrating, due to the limited availability of effective drugs. One of the main reasons for this is the fact that many of the drugs that are effective against human herpes virus

are not effective against feline herpes virus. The cost of the drugs and the need for frequent administration are additional factors that prevent owners from providing optimal treatment to their cats.

Clinically proven drugs

1. Trifluridine - very effective against feline herpes, and is available commercially in many countries. However, it is topically irritating and the recommended dose is every 2 hours, which makes compliance very difficult.
2. Idoxuridine - slightly less effective against feline herpes virus than trifuridine. Also, it is not available commercially, and must be compounded by special pharmacists. However, it is less irritating and needs to be given 'only' 4 times/day.
3. Vidarabine - less effective than idoxuridine, and even more difficult to obtain (can be compounded as a 3% ointment), but well-tolerated in cats.

Ineffective or contraindicated drugs

1. Acyclovir is a commonly-used drug in the treatment of human herpes infections. However, the effective dose against feline herpes is x80 the dose in humans, making this drug ineffective in cats.
2. Bromovinyldeoxyuridine - not effective against feline herpes virus
3. Valacyclovir - contraindicated in cats due to bone marrow supporession, s well as hepatic and renal toxicity.
4. Steroids should not be used in the treatment of feline herpes conjunctivitis, as they may increase the activity of latent viruses and exacerbate the infection.

The future?

1. A number of drugs have been shown to be effective against feline herpes in vitro, but have yet to be tested *in vivo* or in clinical trials. These include:

- Ganciclovir
- Cidofovir
- Penciclovir

2. L-lysine - preliminary studies show that L-lysine given orally (500 mg, twice daily) may be effective in treatment of feline herpes virus. The drug inhibits viral replication by competing against arginine.
3. Interferon - there are reports that the drug (administered orally or topically) may be an effective treatment.

Neuroprotective treatment in glaucoma

Glaucoma is a common, and painful, cause of blindness. For many years the disease was defined as an elevation in intraocular pressure (IOP). However, today there is increasing recognition that additional factors, besides elevated IOP, also play a role in the progressive loss of vision that characterizes glaucoma. These factors may be the reason why glaucomatous damage develops in many normotensive patients, and may account for the fact that in other patients loss of vision progresses even after IOP has been successfully lowered. Similar pathogenesis of axonal damage, which progresses even after the initial insult has been alleviated, is observed in many neurologic disorders including stroke, hypoglycemia, trauma and epilepsy. There is growing evidence that in these, and other, diseases, progressive axonal damage is the result of secondary degeneration. It is suggested that axons damaged by the initial insult release various substances into their immediate surroundings. The localized high concentrations of these substances create a hostile micro-environment. Adjacent axons, which were not damaged during the initial insult, undergo secondary degeneration as a result of being immersed in this toxic milieu. This creates a "domino effect" in which (in the case of glaucoma) optic nerve axons will continue to degenerate even after IOP has been successfully lowered, resulting in further loss of vision.

In searching for mediators of secondary degeneration, much of the attention has focused on the role of glutamate, an amino acid that normally functions as an excitatory neurotransmitter in the central nervous system. However, following neuronal injury, intracellular glutamate is released by damaged axons into the immediate surroundings. The resulting locally-elevated concentration of glutamate causes overstimulation of glutamate receptors in neighbouring (undamaged) neurons. This stimulation (excitotoxicity), in turn, leads to increased calcium influx, thereby starting an intracellular enzymatic cascade progressing to apoptosis and cell death. Therefore, it follows that compounds which inhibit glutamate may slow or stop the cascade of secondary degeneration, and protect the undamaged neighbouring axons. This therapeutic approach, known as neuroprotection, is being studied in a number of acute and chronic neurological disorders; some neuroprotective compounds are in advanced testing stages in humans.

There is growing evidence that glutamate also plays an important role in the progressive loss of vision in glaucoma patients, and that this damage may be attenuated by glutamate receptor antagonists. Elevated glutamate levels have been demonstrated in rats with partial optic nerve lesion. Inhibition of glutamate receptors, using memantine, resulted in decreased secondary degeneration and protection of the optic nerve. Further proof for the toxic role of glutamate in axonal death was the intravitreal injection of glutamate in mice and rats. These injections resulted in glaucomatous-like damage to the retina and optic nerve, damage which was once again prevented by memantine. Glutamate's role in optic neuropathy is not restricted to induced nerve damage. Elevated glutamate levels have been demonstrated in the vitreous of glaucomatous rabbits, dogs and humans. Therefore, the testing of neuroprotective drugs in glaucomatous patients is warranted. Obviously, such

drugs are not expected to restore vision which has been lost prior to initiation of treatment. However, it is hoped that neuroprotective therapy will prevent (or decrease) damage to additional optic nerve fibers, and thereby halt (or slow down) the progressive loss of vision that is the scourge of glaucoma.

Science fiction? Restoring vision in the blind patient

Several approaches are being developed to restore vision to blind patients. These approaches have yielded promising results in patients suffering from (inherited) diseases of the outer retina. Therefore, they could potentially be used to restore vision in patients suffering from PRA (prcd), congenital stationary night blindness, etc.

Two therapeutic approaches are being tested. The first approach is based on restoring function to the photoreceptor by replacing the defective gene. This can be done using genetic engineering methods, which involve inserting the missing gene onto a modified virus and injecting it subretinally. Such studies have been conducted in dogs with various forms of inherited photoreceptor diseases by Dr. G Aguirre (Cornell/Pennsylvania) and Dr. K Narfstrom (Missouri). The operations have restored vision (proven both behaviorally and using ERG) in a large number of dogs, with some patients already monitored for 3-4 years post-surgery. Photoreceptor function can also be restored following subretinal injections of stem cells or RPE basement membrane.

A second therapeutic approach involves use of retinal implants. These are miniaturized electrodes that are implanted on the surface of the retina. The electrode receives visual input either from light sensitive diodes or from a miniature camera (mounted on glasses). The visual input is translated into electrical currents that stimulate the ganglion cells and generate a neuronal signal. The technology is in its preliminary stages, and is severely limited by the number of electrodes that can be implanted (thus affecting visual resolution), but has already been used on humans (and dogs!). See www.2-sight.com for more details.

Recommended reading

1. *Ofri R, et al. Clinical evaluation of pimecrolimus eye drops for treatment of canine keratoconjunctivitis sicca: A comparison with cyclosporine A. Vet J 2007; in press (e-published October 18, 2007).*
2. *Berdoulay A, et al. Effect of topical 0.02% tacrolimus aqueous suspension on tear production in dogs with keratoconjunctivitis sicca. Vet Ophthalmol. 2005;8:225-32.*
3. *Brooks DE, Ollivier FJ. Matrix metalloproteinase inhibition in corneal ulceration. Vet Clin No Am, Sm Anim Pract 2004;34:611-22.*
4. *Maggs DJ. Update on pathogenesis, diagnosis, and treatment of feline herpesvirus type 1. Clin Tech Small Anim Pract. 2005;20:94-101.*
5. *Chidlow G, et al. Pharmacological neuroprotection for glaucoma. Drugs. 2007;67:725-59.*
6. *Ofri R, Narfström K. Light at the end of the tunnel? Advances in the understanding and treatment of glaucoma and inherited retinal degeneration. Vet J 2007;174:10-22.*