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Case Report

# GLS-1027 to Treat Anterior Uveitis in a Cavalier King Charles Spaniel Dog

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## Abstract

Non-infectious, autoimmune anterior uveitis is a significant cause of ocular disease in both dogs, horses, and humans with the potential for significant vision loss. The mainstay of treatment is topical and/or systemic corticosteroids, however, animals, similar to humans, are not uncommonly resistant to therapy. Additionally, prolonged corticosteroid treatment may cause systemic and ocular toxicity. We describe here a case of steroid-resistant uveitis successfully treated with GLS-1027, an immunomodulatory compound that inhibits Th17 maturation and release of multiple inflammatory cytokines involved in the pathogenesis of uveitis. GLS-1027 may provide an alternative as a steroid-sparing therapeutic option.

## Introduction

Non-infectious, anterior uveitis is a significant cause of ocular disease in dogs, horses, humans, and other species that has the potential to lead to vision loss and blindness. While the disease is most commonly considered as autoimmune for humans and the most common etiology in dogs [1,2] infectious disease neoplastic etiologies must also be considered [2,3]. In all species, the primary goal of treatment is sight preservation with secondary goals to limit pain, discomfort, photophobia, and in dogs minimizing secondary sequelae such as posterior synechia [3]. In animals, topical corticosteroid treatment combined with topical mydriatics with or without the use of systemic anti-inflammatory medications represents the standard of care for anterior uveitis [2,4]. While immunosuppressives are considered the standard for steroid-resistant disease in humans [5], these are seldom used in animals due to toxicity and cost. Studies in animals have reported that approximately 1-35% of the total topical corticosteroid dose is systemically absorbed, [4] and may result in systemic side effects, including endocrinopathies [3]. Steroid-induced ocular pathology, including the development of glaucoma, cataract formation, and keratopathy are not uncommon in dogs with prolonged corticosteroid use [4] with a similar side effect profile for humans. Therefore, a safe and effective alternative to corticosteroid treatment for chronic recurrent idiopathic uveitis is warranted. Autoimmune uveitis in humans [6] and horses [7,8] has been attributed to Th17 mediated pathology with a complex interplay between a number of inflammatory cytokines including TNFα and IL-6. GLS-1027, [S,R]-3-phenyl-4,5-dihydro-isoxazoleacetic acid, is a small molecule compound with anti-inflammatory activity currently in clinical development. GLS-1027 is a potent inhibitor of lipopolysaccharide (LPS)-induced inflammation characterized by normalization of levels of the cytokines tumor necrosis factor (TNFα), interleukin (IL) 1β, and IL-6 both in vitro and in murine animal models [9-12]. Additional unpublished data has shown that GLS-1027 inhibits IL-17 and IL-23 mediated activation and downregulates Th17 T cells.

In this paper, we describe a case report of the use of GLS-1027 to treat canine uveitis.

## Case Report

A 5-year-old intact female Cavalier King Charles Spaniel developed light sensitivity, progressive episcleral injection, conjunctival hyperemia, peripheral perilimbal corneal edema, generalized swelling of periocular tissue, and mucoid ocular discharge starting from the seventh week of her 3rd pregnancy. A similar episode had occurred during her 2nd pregnancy that spontaneously resolved within a few days after whelping (post-partum); an ultrasound during pregnancy was without evidence of pathology.

Ophthalmologic examination 33 days post-whelping, documented bilateral moderate to severe conjunctival hyperemia, moderate to severe episcleral injection, 360-degree corneal perilimbal edema and dense circumferential perilimbal neovascularization extending 2 mm from the limbus (ciliary flush). She had bilateral faint inferior keratic precipitates adhered to the corneal endothelium. The anterior chamber was clear and the iris, lens, vitreous, and fundus were unremarkable. Laboratory evaluation including complete blood count, complete metabolic profile, and serologies for Lyme borreliosis, Bartonella, Brucella, Cryptococcus, Neospora, RMSF (PCR), and Toxoplasma, Ehrlichia, and Anaplasma were normal or negative. A diagnosis of bilateral anterior uveitis was made. Treatment was initiated with carprofen 37.5 mg orally once daily, 1% prednisolone acetate (1 drop OU, TID) and atropine ointment (1/4" strip OU, daily). Treatment resulted in a rapid decline in mucus production and light sensitivity, but a slow decline in perilimbal edema, with a minimal to moderate decrease in episcleral injection and conjunctival hyperemia over the following few weeks. A recheck ophthalmic examination performed 53 days post-whelping demonstrated resolving uveitis. Topical corticosteroids were reduced to twice daily and then to once daily without evidence of worsening, however, attempts to further reduce the frequency topical steroid treatment resulted in a rapid flare-up of clinical signs. Over the ensuing three months, topical steroids were continued with minimal to modest improvement of conjunctival hyperemia, episcleral injection, and peripheral corneal edema. After informed consent provided by the owner, treatment with 3 mg/kg of GLS-1027 was initiated on day 123 post-whelping at a dose of 3 mg/kg daily (30 mg/day for a 10 kg dog) administered daily as a powder mixed in food each morning. Ophthalmologic symptoms significantly improved within three days and topical corticosteroids were reduced from daily to three times a week (TIW) without clinical worsening. However, attempts to further reduce corticosteroid exposure were unsuccessful. Ophthalmologic examination four weeks after GLS-1027 therapy was started, confirmed the owner's findings; Topical steroid usage was maintained at TIW. At 184 days post-whelping GLS-1027 was changed to 3 mg/kg twice daily. Within 7 to 10 days there was complete resolution of residual episcleral injection, corneal edema, and a general brightness returned to her eyes according to her owner. At 215 days post-whelping topical steroids were tapered to twice weekly and then discontinued completely 30 days later without recurrence. Throughout the treatment period of GLS-1027 treatment, there was no change to the dog's activity, eating habits, or weight. Ophthalmologic examination at 282 day post-whelping, showed resolution uveitis and no abnormalities on hematologic and serum biochemistry panels.

## Discussion

This case report represents the first veterinary clinical use of the immuno-modulatory drug GLS-1027 for the treatment of steroid-resistant non-infectious uveitis. As presented, treatment with topical steroids achieved only partial resolution of ophthalmic findings. Addition of GLS-1027 at 3 mg/kg given orally, once daily allowed for a reduction of topical steroids to TIW. An increase of GLS-1027 to 3 mg/kg twice daily was associated with complete resolution of any residual ophthalmologic pathology and allowed for steroid discontinuation without symptom recurrence. Throughout five months of treatment, GLS-1027 was well tolerated without evidence of clinical adverse effects or abnormal laboratory findings. Both human disease and animal models of experimental autoimmune uveitis (EAU) have demonstrated the critical role of Th17 T cells and Th17 family of cytokines, IL-17, IL-23, IL-6, and TNFα, having displaced the theory of a Th1 dominant pathway in the pathogenesis in this disease [6]. The pathogenesis of recurrent equine uveitis (ERU) has similarly been shown to be mediated by Th17 cells and associated with increased production of IL-17 [8], that has also displaced a theory of a dominant pathologic Th1 T cell-induced pathology [13]. Further support of a Th17 mediated disease in horses with ERU is gained from a study of banked globes that demonstrated strong immunohistochemical staining for IL-6, IL-17, and IL-23 in the cytoplasm of nonpigmented ciliary epithelial cells and mononuclear cells infiltrating the iris and ciliary bodies [7]. Unfortunately, there has not been a similar advancement in elucidating the underlying inflammatory pathways associated with non-infectious uveitis in dogs.

Corticosteroid therapy is currently the main treatment for uveitis in canines [4], however, prolonged use is associated with significant toxicity. Whereas immunosuppressives and/or anti-cytokine monoclonal antibody agents are recommended for steroid resistant disease in humans [5], the cost, risk of infection, and other potential adverse effects precludes other than rare veterinary use of these agents. Moreover, studies in humans may support a multi-factorial approach targeting multiple inflammatory cytokines versus blockade of a single cytokine may be required for the treatment of idiopathic uveitis as clinical trials of anti-IL-17 monoclonal antibodies did not demonstrate efficacy

against human recurrent uveitis [14]. In the Lewis rat model of LPS-induced experimental autoimmune uveitis, GLS-1027 at 25 mg/kg was as effective as systemic dexamethasone treatment in preventing cellular infiltration into the anterior chamber [10]. Clinical activity correlated with GLS-1027 mediated inhibition of NF-κB translocation in ocular homogenates and decreases in TNFα levels in the aqueous humor [10]. The immuno-modulatory activity of GLS-1027 is associated with inhibition of multiple inflammatory cytokines including IL-1β and IL-6 [15,16] with unpublished studies demonstrating inhibition of Th17 maturation and decreased release of IL-17 and IL-23. GLS-1027 may therefore be an alternative to corticosteroid treatment in canines with chronic or recurrent idiopathic uveitis. In single ascending dose and 28-day multi-dose level GLP toxicokinetic studies, the plasma half-life for GLS-1027 for dogs ranged between 3 and 5 hours [17] that would support either daily or twice daily dosing. We found that, while once daily treatment provided a modest clinical benefit and allowed some reduction in corticosteroid treatment frequency, greater clinical benefit was realized with twice daily dosing. In these studies, GLS-1027 was well tolerated without clinical, histologic, or laboratory abnormalities, and had a maximal tolerated dose of GLS-1027 in dogs was 100 mg/kg, far greater than the 6 mg/kg daily exposure in this study. A separate study showed no evidence of cardiac toxicity. In humans, GLS-1027 had 85-90% oral bioavailability and was excreted unchanged in the urine without evidence of hepatic metabolism [17], further supporting oral dosing. In conclusion, this case study showed that GLS-1027 provided significant clinical benefit for the treatment of uveitis in a Cavalier King Charles Spaniel dog. Further clinical studies are planned to determine the utility of GLS-1027 for the treatment of uveitis.

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