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PILOT STUDY

ALVAC-fIL2, a feline interleukin-2 immunomodulator, as a treatment for sarcoids in horses: A pilot study

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Abstract

Background: Sarcoid tumors are common in horses and may negatively impact the performance and value of the horse. No known treatment is reliably successful.

Hypotheses/Objectives: To determine tolerability, overall response rate, time to response, and progression-free survival of horses with biopsy-confirmed or suspected sarcoids treated with ALVAC-fIL2.

Animals: Client-owned horses with measurable, presumed- or biopsy-confirmed sarcoid tumors.

Methods: Prospective pilot study. One milliliter of ALVAC-fIL2 was injected into 4 to 5 areas of the sarcoid(s) in each horse (week 0); this treatment was repeated in weeks 1, 3, and 7. Sarcoids were measured at each visit, and response to treatment was determined according to the Response Evaluation Criteria in Solid Tumors for dogs (v1.0). After the final treatment, horses were reassessed and sarcoids remeasured every 3 months until tumor progression or for a minimum of 1 year if progression was not documented.

Results: Fourteen horses were included. Tumor size decreased in 86% of the horses, and the median time to first response was 89 days (range, 34-406 days). Median time to best response was 211 days (range, 56-406 days), but 3 of the sarcoids still were decreasing in size at the time of final evaluation. The median progression-free interval was not reached. Adverse events were minimal and included transient focal inflammation in 2 horses.

Conclusions and Clinical Importance: Intratumoral injection of ALVAC-fIL2 has promise as a well-tolerated and effective, tissue-sparing treatment for horses with sarcoid tumors.

KEYWORDS
equine, immunotherapy, sarcoid, treatment

Abbreviations: AE, adverse event; ALVAC-fIL2; Oncept IL-2, Feline Interleukin-2 Immunomodulator, Live Canary pox Vector; CR, complete response; IL-2, interleukin-2; ORR, overall response rate; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; UGA, University of Georgia.

1 | INTRODUCTION

Sarcoid tumors are the most commonly diagnosed cutaneous neoplasms in the equine species. Their behaviors range from occult, slowly progressive lesions to sarcoma-like tumors that invade the SC tissues. In many cases, sarcoid tumors decrease the value and use of the horse.[1-3] Treatments include benign neglect, surgical removal, local immunotherapy, radiation therapy, and chemotherapy.[2,4-11] These treatment modalities however have produced mixed outcomes, and for some (eg, radiation therapy) special instrumentation, training, or both is required.[2]

Interleukin-2 (IL-2) is a cytokine signaling molecule with direct effects on T lymphocytes, resulting in their activation and differentiation into lymphocyte-activated killer cells. When administered systemically, it causes unwanted adverse effects such as flu-like clinical signs, hypotension, and capillary leak syndrome. However, these effects may be mitigated by the use of localized, intratumoral administration.[12-14] Feline Interleukin-2 Immunomodulator, Live Canarypox Vector (ALVAC-fIL2; Oncept IL-2, Merial Inc/Boehringer Ingelheim Animal Health, Athens, Georgia) employs ALVAC, an attenuated canarypox vector system, to deliver feline IL-2 intratumorally.

Interleukin-2 has been used to treat cancer in several species including humans, dogs, and cats.[15-19] It also has been used to treat sarcoid tumors in horses.[13,14] Investigators in Germany reported the safe use of intralesional ALVAC-fIL2 in horses with sarcoids, with an efficacy rate of 50% when administered twice, 7 days apart.[20]

The purpose of our proof-of-concept study was to determine the overall response rate (ORR), time to response, and progression-free survival of horses with biopsy-confirmed or suspected sarcoids treated with ALVAC-fIL2 using 4 doses. We hypothesized that intratumoral injection of ALVAC-fIL2 would significantly decrease the size of sarcoid tumors over time, with low risk of adverse events (AEs). Our long-term goal is to develop a safe and effective treatment alternative for horses with sarcoid tumors.

2 | MATERIALS AND METHODS

2.1 | Case selection criteria

Horses of any age, breed, or sex with measurable, presumed- or biopsy-confirmed sarcoid tumors of any clinical morphology, presented to the University of Georgia (UGA) Veterinary Teaching Hospital or Maggie's Menagerie Veterinary Services were eligible for inclusion in this prospective proof-of-concept study. Based on history, physical examination, CBC, and serum biochemical profile results, horses were required to be otherwise clinically healthy. Prior treatment of the sarcoid was acceptable, but disease progression after prior treatment was required. Treatment using a nonsteroidal anti-inflammatory drug was permissible, but horses could not receive prednisolone or other immunomodulatory drugs during the study period. The study protocol was approved by the UGA Clinical Research Committee (Institutional Animal Care and Use Committee for client-owned animals), and signed informed consent was obtained from all owners before study entry.

2.2 | Study schedule

Once the horse was enrolled, the target lesion (ie, the sarcoid to be treated) was identified, photographed, and measured in millimeters. Target lesion location and size were recorded. The sarcoid was injected on day 0 with 1.0 mL of ALVAC-fIL-2 divided into 4 to 5 areas around the tumor using a 20-gauge of smaller needle and Luer-lock syringe. One milliliter was used regardless of tumor size. If >1 target lesion was identified, the 1.0 mL was divided between target lesions. These treatments were repeated on days 7, 21, and 49 (ie, weeks 1, 3, and 7). If needed to minimize stress and possible pain, sedation (eg, xylazine, dexmedetomidine, butorphanol) was administered in accordance with the attending clinician's preference. Physical examination, CBC, and serum biochemical profiles were reevaluated in week 11. Thereafter, physical examinations were performed every 3 months for the duration of the study (Table 1). Horses were required to return to UGA or Maggie's Menagerie Veterinary Services for each scheduled visit; the study period for each horse was 12 months after enrollment or until clear evidence of disease progression was observed.

2.3 | Response to treatment

To evaluate response to ALVAC-fIL2 treatment, target lesions were measured at each visit and compared to baseline (day 0) tumor measurements. Responses to treatment were determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) for dogs (v1.0). The longest diameter of the tumor was recorded. The following RECIST definitions were used: complete response (CR)—disappearance of the tumor; PR—at least a 30% decrease in the longest diameter of the tumor; progressive disease (PD)—a 20% increase in the longest diameter of the tumor; and stable disease (SD)—insufficient shrinkage to qualify for PR and an insufficient increase to qualify as PD.[21] Responses to immunotherapy can cause transient increases in tumor size because of immune cell infiltration and inflammation, and consequently PD was not assessed before week 11.

Time to first response was defined in days from week 0 (ie, first treatment) until the documentation of at least PR. Progression-free survival was defined in days from week 0 until the documentation of at least PD.

2.4 | Occurrence and severity of AEs

All AEs were defined using a modified version of the Veterinary Cooperative Oncology Group Common Terminology Criteria for Adverse Events (v1.1), in which AEs are graded as minimal, mild, moderate, severe, and death related to AE.[22] Horses were closely monitored for immediate AEs to treatment for ≥30 minutes after injection.

TABLE 1 Study schedule

	History and physical examination	Tumor measurements	Complete blood count/ biochemical profile	ALVAC-fIL2 injections
Preenrollment	*	*		
Day 0	*	*	*	*
Week 1	*	*		*
Week 3	*	*		*
Week 7	*	*	*	*
Week 11	*	*		
Week 23	*	*		
Week 35	*	*		
Week 47-52	*	*		

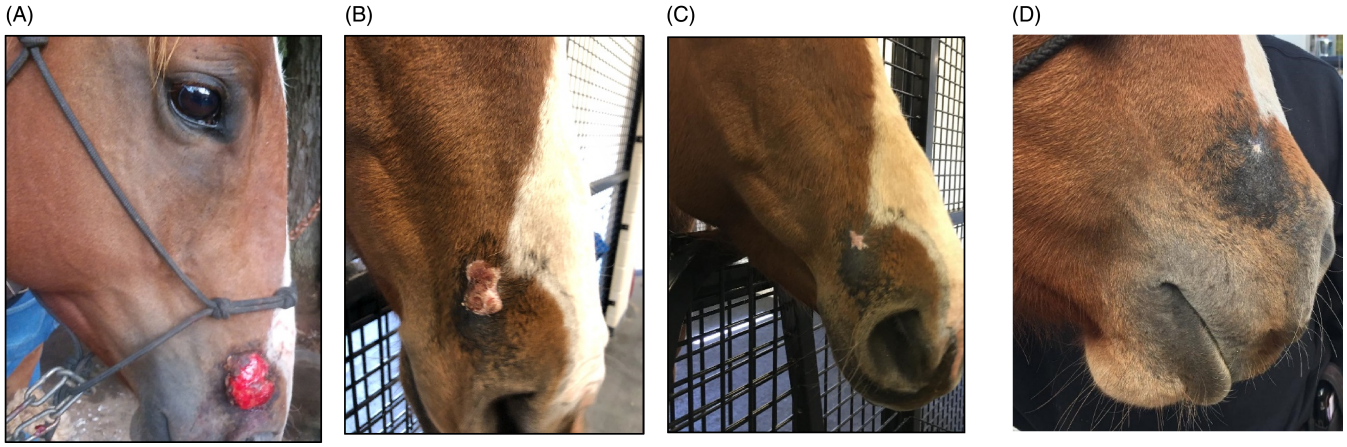

FIGURE 1 A, Biopsy-confirmed sarcoid pretreatment; B, immediately before ALVAC interleukin-2 treatment in week 7; C, at 6 months; and D, at 12 months

Nonimmediate AEs were assessed by history and physical examination at each visit and repeat CBC and serum biochemical profile at week 11.

3 | RESULTS

Fourteen horses were included. Patient and tumor characteristics are summarized in Supplemental Table S1. Median age was 10.5 years (range, 2-19 years). Tumors were located on the trunk (n = 6), ear (n = 5), and muzzle or face (n = 3). Median baseline tumor diameter was 35 mm (range, 12-110 mm). Median number of treated sarcoids per horse was 1 (range, 1-2). One horse, a 13-year-old Thoroughbred Gelding, had coalescing tumors encircling the right ear making precise tumor measurements and determination of number of tumors difficult.

Median number of treatments administered was 4 (range, 2-5). The ORR was 86%, and the median time to first response was 89 days (range, 34-406 days). Best responses included 7 CR (50%), 5 PR (35%), 1 SD (7%), and 1 PD (7%). Median time to best response was 211 days (range, 56-406 days), but 3 of the sarcoids assessed as PR were decreasing still in size at the time of final evaluation. Examples of tumor responses are presented in Figure 1. The horse that experienced SD was prematurely withdrawn from the study at week 11 at the owner's request, and the sarcoid was surgically excised. Two horses received <4 treatments for the following reasons: (a) CR after 3 treatments and (b) injection site inflammation after the second treatment. This particular horse ultimately had a CR with only 2 treatments. Two horses received >4 treatments in an attempt to improve their responses. At the time of the last visit, the best response in both horses was PR. Median progression-free interval was not reached. Median follow-up time for all horses was 380 days (range, 76-432 days).

All injections were well tolerated, aside from transient, mild to moderate (grade 1-2) focal inflammation in 2 horses. One horse, with a sarcoid on its rostral muzzle, developed swelling, erythema, unilateral epiphora, and serous nasal discharge within 30 minutes of its second treatment. The airway remained patent. The horse was treated with 1 dose of flunixin meglumine (Banamine, Merck Animal Health, Madison, New Jersey) and according to the owner, returned to normal within 24 hours (Figure 2). The other horse's inflammation reportedly developed 1 to 2 days after the final treatment. The owner reported

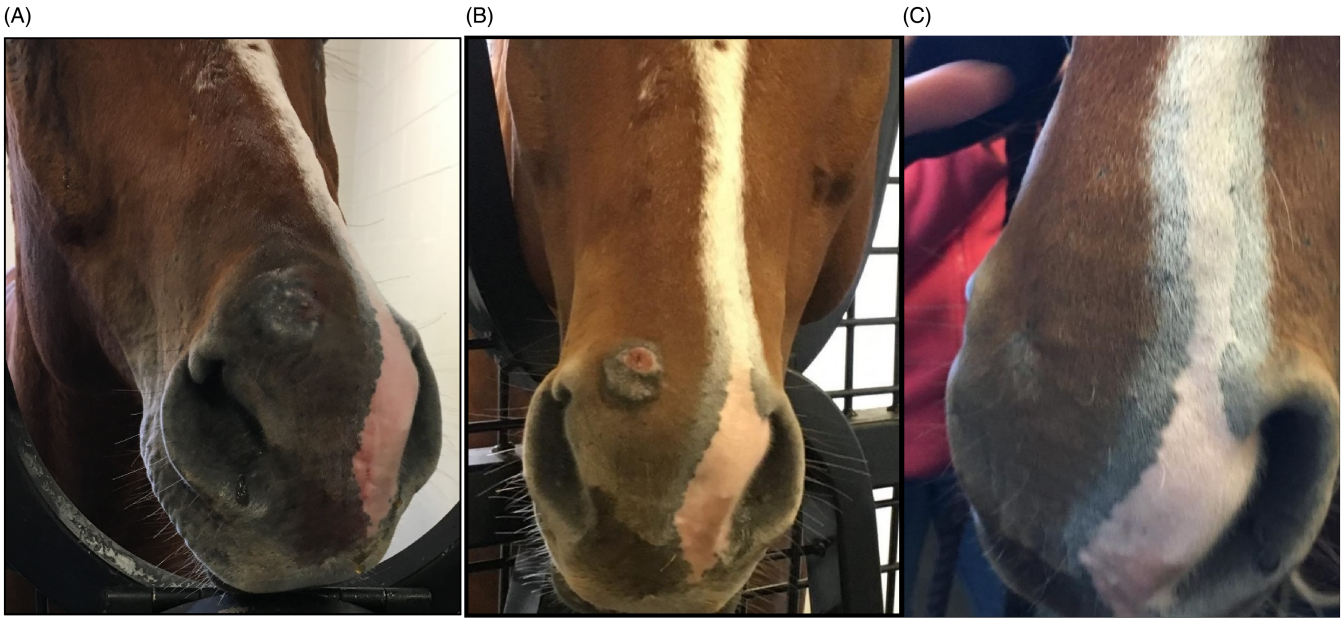

FIGURE 2 A, Local reaction in presumed sarcoid, 15 minutes after treatment #2 (week 7); B, 1 month later; and C, at final visit

that the horse developed erythema and pain that resolved with no treatment within 24 to 48 hours. One horse developed leukotrichia at the sarcoid site after experiencing a CR; the hair color had returned to normal by the next 3-month reevaluation. No changes in hematologic or biochemical results were noted during treatment.

4 | DISCUSSION

Results of our proof-of-concept study provide evidence that ALVAC-fIL2 is a safe and cosmetic treatment for sarcoids in horses. The ORR was 86%, 50% of which were CR. Median time to first response was 89 days; median time to best response was 211 days.

Various treatments have been used for sarcoids, but none has been predictably successful. Some options, such as surgical excision, may require general anesthesia, can be disfiguring or painful, or both without guarantee of complete tumor excision or long-term control. Additionally, surgical removal is usually most successful when coupled with adjunctive treatment.[3,6,23,24] Removal using a carbon dioxide laser appears to be well tolerated, with up to 81% of horses free of recurrence at 12 months.[3,7,25] However, this option requires expensive equipment and special training, limiting its use. Cryotherapy carries a high risk of AEs including swelling, hyperemia, hemorrhage, local edema, and necrosis. General anesthesia may be required, and multiple treatment sessions may be required. Furthermore, ensuring proper freeze-thaw cycles to the necessary temperatures can be difficult, leading to inconsistent results.[3,6,26] Immunotherapy options have included Bacillus Calmette-Guérin and imiquimod cream. Bacillus Calmette-Guérin is derived from *Mycobacterium bovis* and injected directly into sarcoids to stimulate a cell-mediated response to induce tumor regression. It appears to work well for periocular sarcoids. However, potential AEs include extensive swelling within minutes to hours that progresses to necrosis and ulceration, fever, and general malaise. There is also a risk of anaphylaxis.[3,27-29] Imiquimod cream is an immune-response modifier used to treat actinic keratoses and genital warts in humans. It also can cause pain, erythema, and erosion of the treated area.[8] A previous study determined that acyclovir, an antiviral used primarily in the treatment of herpes virus in people, is no more effective than placebo.[4] Finally, radiation therapy (most commonly brachytherapy) and intralesional or topical chemotherapy have been used, but the risks of personnel exposure to radiation and hazardous drugs must be considered.[3,6,9,10]

Cancer immunotherapy, which recruits the patient's own immune system to control and eradicate the neoplasm, has become increasingly popular in both human and veterinary oncology. There are various treatment approaches, 1 of which involves vaccines that incorporate viral vector systems carrying immunostimulatory cytokines. These viral vectors are highly attenuated and replication-defective; they can infect cells, insert specific gene sequences, and stimulate innate and adaptive immune responses (specifically T-cell responses) without the risk of viral dissemination throughout the patient, environment, or both. Once the patient's cells are infected, the cytokine carried by the viral vector is produced at high concentrations at the tumor site. Because systemic concentrations of the cytokine remain low, the risk of adverse systemic events is substantially decreased.[30-32]

A commonly used viral vector system is ALVAC, an attenuated canarypox vector system. It is a genetically and physically stable

ubiquitous vector with high biosafety and is nonreplicative in mammals. Several ALVAC-based licensed veterinary vaccines are commercially available and widely used in disease prevention. Among these are Recombitek, Purevax, Eurifel, and Proteqflu vaccines.[33] Studies completed in animals and humans indicate that ALVAC vectors are well tolerated and that immune responses or protective immunity against challenge with the cognate pathogens can be induced.[34-37]

Interleukin-2 is a cytokine-signaling molecule with direct effects on T lymphocytes, resulting in their activation and differentiation into lymphocyte-activated killer cells. Interleukin-2 is used in the treatment of melanoma and renal cell carcinoma in people.[15-17] When administered systemically, it causes unwanted adverse effects such as flu-like clinical signs, hypotension, and capillary leak syndrome. However, these effects may be mitigated by the use of localized, intratumoral administration.[12]

Feline Interleukin-2 Immunomodulator, Live Canary pox Vector (ALVAC-fIL2, Oncept IL-2) employs the ALVAC vector system to deliver feline IL-2. It is licensed in the European Union for the postsurgical treatment of cats with fibrosarcoma as an adjunct to surgery and radiotherapy. The immunotherapeutic has been evaluated in the United States but, at the time of this writing, is not commercially available. It is well tolerated in cats and results in a longer median time to tumor recurrence when combined with surgery and brachytherapy than when the latter treatments are used alone.[35,36]

The use of IL-2 in the treatment of sarcoid tumors in horses is not novel. One clinical study reported significantly improved CR rate with the use of local cisplatin plus a single high dose of IL-2 as compared to 5 or 10 low doses of IL-2 alone (53% vs 14%, respectively).[14] Local application of tumor lysates loaded with autologous dendritic cells or human recombinant IL-2 in horses with sarcoids and squamous cell carcinoma also has been proven safe.[13] A recent study reported the safety and efficacy of ALVAC-fIL2 for the treatment of sarcoids in horses. Twenty horses were included in that prospective study. Unlike our protocol, the tumors were injected twice, 7 days apart. Only transient fever developed in 1 horse after treatment; ORR to ALVAC-fIL2 was only 50%.[20]

The finding of delayed responses, with median times to first and maximal responses of 89 and 211 days, respectively, is not surprising. Immunotherapy requires recruitment a patient's immune system to control and eradicate tumors, which takes time to occur. In some cases, tumors may transiently get larger, in part because of immune cell infiltration.

Because of the small number of horses in our study, it is difficult to determine predictors of response. One may assume that larger tumors would be less likely to respond. However, the horse with the largest tumor (a 110 mm biopsy-confirmed sarcoid) experienced a CR. Extent of pretreatment may play a role, because the horse with the most intensively pretreated sarcoid experienced PD, progressing rapidly by week 11. Admittedly, the possibility of spontaneous regression, especially in the younger horses, cannot be discounted. A study of sarcoids in a group of young horses (age 3 years) followed over the course of 5 to 7 years, found that 62% became sarcoid-free during the follow-up period.[11] The median age of horses in our study cohort was 10.5 years, and responses were seen in older horses. Nonetheless, additional studies are required to answer these questions.

Limitations of our study are its small sample size and lack of a placebo control. Lack of a histologic diagnosis in some cases must be noted as well. In the field, sarcoids often are diagnosed solely based on clinical appearance. However, a previous study investigated the accuracy of this diagnostic approach, and a success rate of 82% with sensitivity of 83.3% and specificity of 79.6% were found.[38] Another challenge was defining CR. None of the horses had posttreatment biopsies to ensure all tumors were gone. It was impossible to determine if horses with residual alopecia in the area had residual disease. To avoid overestimation of ORR, CR was defined as complete resolution of the sarcoid with regrowth of hair in alopecic areas. If a mass resolved, but alopecia persisted, the response was considered a PR. Nonetheless, the results of our pilot study are encouraging and provide justification for larger, placebo-controlled trials.

In conclusion, our results provide evidence that ALVAC-fIL2 is a safe, cosmetic, and effective treatment for sarcoid tumors in horses. Furthermore, our results provide a basis for a larger, placebo-controlled study to better define the role of this treatment in sarcoid tumors in horses.

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CONFLICT OF INTEREST DECLARATION

Drs Grosenbaugh and Leard were employed by Boehringer Ingelheim Animal Health at the time this study was performed.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

The study protocol approved by the University of Georgia Clinical Research Committee (IACUC for client-owned animals); signed informed consent was obtained from all owners prior to study entry.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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