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Response to tigilanol tiglate in dogs with mast cell tumors

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Abstract

Background: Information regarding response rate to tigilanol tiglate for mast cell tumors in dogs is limited.

Objectives: Report the response rate and durability of tigilanol tiglate intratumoral treatment in dogs with mast cell tumors presented to veterinary oncologists.

Animals: One hundred forty-nine dogs; 151 individual tumors.

Methods: Multicenter, retrospective survey-based study. Veterinary oncologists subscribed to the American College of Veterinary Internal Medicine (ACVIM) oncology listserv were solicited for information from dogs treated with tigilanol tiglate. An electronic survey was used to collect information at initial treatment, 1 month and 1 year after treatment.

Results: Most tumors were cutaneous, occurred on the limbs and were cytologically low grade. Seventy-five percent of dogs achieved a complete response after 1 dose of tigilanol tiglate 1 month after treatment. This response was durable at 1 year in 64% of dogs for which data were available (n = 88). Wound formation, an expectation after treatment, occurred after a median of 7 days (range, 1-91 days), with a median wound area of 4.71 cm^2 (range, 0.09-100 cm^2). Wounds took a median of 30 days to heal completely (range, 14-154 days). A moderate association between tumor volume and wound size was confirmed.

Conclusions and Clinical Importance: Tigilanol tiglate is an effective local treatment option for mast cell tumors in dogs with a predictable clinical course and response. Because of the unique mode of action and clinical course, client education and careful case selection is necessary before electing tigilanol tiglate for local treatment.

KEYWORDS
canine, EBC-46, intratumoral, mast cell tumor, Stelfonta

1 | INTRODUCTION

Mast cell tumor (MCT) is the most common skin tumor in dogs,[1] can involve the dermis, subcutis, or both, and exhibits variable biological behavior, which can be difficult to predict.[2] Standard treatment for a localized, nonmetastatic MCT is surgical excision.[3] Even with

Abbreviations: ACVIM, American College of Veterinary Internal Medicine; CR, complete response; FDA, Food and Drug Administration; MCTs, mast cell tumors; REDCap, Research Electronic Data Capture.

incomplete margins, surgery may be curative for low-grade tumors,[4] whereas additional local treatment (surgical revision or radiation) may be considered for high-grade tumors.[5] If metastatic disease is identified or the tumor is high-grade, chemotherapy is recommended.[6] Although surgical excision is recommended for local control, it can be challenging because of the anatomic location of some MCTs, and occasionally is declined by owners.[7] Thus, alternative options for local treatment are needed.

Tigilanol tiglate (Stelfonta, Virbac, Westlake, Texas) is a novel small molecule extracted from the seed of *Fontainea picrosperma*[8] and approved by the Food and Drug Administration (FDA) for the intratumoral treatment of nonmetastatic cutaneous MCTs and nonmetastatic SC MCTs located at or distal to the elbow or hock in dogs.[9] Preclinical studies confirmed the antineoplastic potential of tigilanol tiglate for the treatment of solid tumors,[10] whereas a case study described its use for a SC MCT in a dog.[11] Subsequent studies further defined the dose of tigilanol tiglate for MCTs in dogs.[8] In a randomized controlled clinical study, 75% (n = 80) of MCT patients experienced complete response (CR) by day 28 after 1 dose of tigilanol tiglate with no recurrence in 93% (n = 59) of patients at 84 days.[12] The formation of a wound, and wound size relative to tumor volume, correlated and were strongly associated with outcome.[12] A follow-up study evaluated the durability of response of the dogs from the initial trial that achieved CR by day 28 after a single tigilanol tiglate injection (n = 85). At 1 year posttreatment, 89% of treated dogs remained tumor-free (n = 64). Of the patients that had tumor regrowth, all recurrences occurred within the 1st 6 months, typically within the 1st 12 weeks after initial treatment.[13] In dogs with cytologically diagnosed high-grade MCT, a single dose of tigilanol tiglate resulted in CR at 28 days after treatment in 44% (8/18).[14]

Much of this initial data was extracted from the original trials, which were highly controlled with strict inclusion criteria, and thus subject to selection bias, which may limit extrapolation of the results to a clinical setting. The clinical use and efficacy of tigilanol tiglate in dogs presented to oncologists, with MCTs in various locations, stage of disease and treatment histories, is unknown. We aimed to better characterize the use of tigilanol tiglate by practicing veterinary oncologists, and to determine the local response and CR rate to tigilanol tiglate in a specialty practice environment. We hypothesized that the local response and CR rate would be lower in a group of patients presented to veterinary oncologists compared with that reported in the initial trial conducted in a primary care practice setting.

2 | MATERIALS AND METHODS

A multicenter retrospective analysis of dogs diagnosed with MCT treated with tigilanol tiglate was completed. Starting in February 2021, American College of Veterinary Internal Medicine (ACVIM) oncology diplomates subscribed to the ACVIM Oncology listserv were solicited for data where tigilanol tiglate was used for the treatment of MCTs in dogs. Study data were collected and managed using REDCap (Research Electronic Data Capture; Vanderbilt University, Nashville, Tennessee) electronic data capture tools hosted at Iowa State University.[15,16] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing: (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources. A REDCap data survey was used to collect information regarding the initial tigilanol tiglate treatment and subsequent surveys were used to collect follow-up data at 1 month and 1 year after treatment. The surveys were generated and distributed after the FDA approval of tigilanol tiglate.

The following data were collected at the initial treatment: signalment (age, sex, breed); location of the MCT; if the MCT was clinically determined to be cutaneous or SC; how the tumor was diagnosed; grade of tumor (cytologic, histologic, or both); if staging was completed (regional lymph node aspirates, abdominal ultrasonography, aspirates of the liver and spleen, chest radiographs, other); if metastatic disease was present and where; if prior treatment was pursued (surgery, radiation therapy, chemotherapy, immunotherapy, electrochemotherapy, or other); tumor measurements (length, width and height in centimeters [cm]); the longest tumor diameter was extrapolated from the 3 provided measurements; tumor volume in cm^3 was calculated by REDCap using the previously reported modified ellipsoid formula where volume = 1/2 [length × width × height][12]); dose of tigilanol tiglate in milliliters; and if sedation or anesthesia was used during administration of tigilanol tiglate. In cases when data regarding multiple tumors on the same patient were collected, it was ensured that the MCTs were located on different areas of the body and that they developed at least 2 months apart to prevent counting a recurrent MCT as a new tumor.

If available, additional data collected at 1 month after treatment included: the response achieved based on the canine response evaluation criteria for solid tumors in dogs (cRECIST v1.0)[17]; if the tumor was retreated at 28 days; if retreated, the response based on cRECIST v1.0 within 1 month of retreatment; if other MCTs developed after the initial treatment at distant sites not considered to be regrowth or associated with the initial tumor; if tigilanol tiglate was used in combination with other treatments (surgery, radiation therapy, immunotherapy, chemotherapy, electrochemotherapy, other); supportive medication(s) given concurrently or at the time of treatment with tigilanol tiglate (antiemetics, antidiarrheals, appetite stimulants, prednisone, H1-blockers, H2-blockers, proton pump inhibitors, pain medications, other); maximum wound size using the ellipse formula as previously reported[18]; time in days between initial tigilanol tiglate administration and maximal wound size; and time in days between initial tigilanol tiglate administration and complete wound healing.

If available, additional data collected at 1 year after treatment included: the response based on cRECIST v1.0 and if there was a change in response from 1 month to 1 year; duration of time in days when a change occurred; if the tumor required retreatment after 30 days; how many times the tumor was treated; and if additional MCT developed after 30 days after initial treatment.

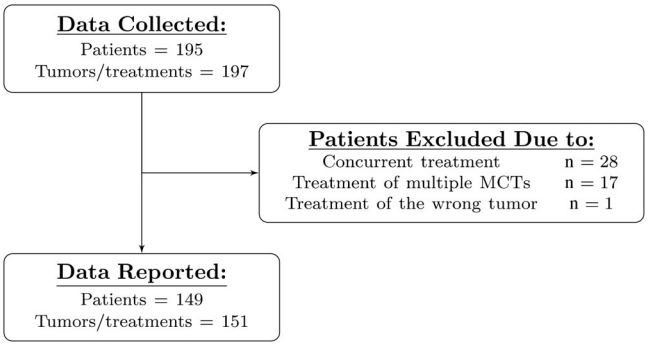

FIGURE 1 Patient retention for dogs with mast cell tumors (MCTs) treated using tigilanol tiglate.

Statistical analysis was limited and generally descriptive in nature. However, to assess the correlation between tumor volume and wound area as calculated by the ellipse formula,[18] a fractional polynomial regression was computed in Excel (Microsoft, 2022). Results of the fractional polynomial regression supported computation of a correlation coefficient of square root of wound area versus cube root of tumor volume.

3 | RESULTS

Data from 195 dogs were collected from February 2021 through March 2023 from 36 individual veterinary oncologists (representing a 6% response rate to the survey; 36/607 members who are subscribed to the ACVIM oncology listserv). Patients that received tigilanol tiglate with other concurrent definitive treatments (surgery, radiation therapy, chemotherapy, electrochemotherapy, or other; n = 28) or that had multiple MCTs treated simultaneously (n = 17) were excluded from analysis. Patients that received other definitive treatment before tigilanol tiglate were included. One patient was excluded because the injected tumor was not a MCT (a lipoma). Thus, data from 149 patients with 151 distinct and temporally separated MCTs are reported in our study (Figure 1). Data available at each time point is outlined in Table 1. There were 61 neutered males, 80 spayed females, 5 intact males, and 3 intact females. Thirty-eight different breeds were represented. The most common breeds included mixes (31%), pit bulls (11%), Labrador retrievers (11%), and boxers (7%). Patients had a median age of 8 years (range, 0.5-19 years) and median weight of 27 kg (range, 1.4-55 kg).

The calculated median tumor volume was available for 145/151 (96%) MCTs and was 0.86 cm^3 (range, 0.004-24.5 cm^3). The median tumor longest diameter was reported for 146/151 (97%) MCTs and was 1.7 cm (range, 0.4-6.2 cm). Sixty-four percent of patients (96/149) had at least 1 diagnostic staging test with 6% (6/96) having confirmed cytologic metastatic disease to the regional lymph nodes (Table 2). The median dose of tigilanol tiglate was 0.44 mL (range, 0.05-5 mL; n = 148). Data about concurrent medications was collected for 79% (119/151 treatments; Table 3). Sedation was used for

TABLE 1 Number of patients and tumors for which data were available at initial data collection, 1 month, and 1 year following treatment with tigilanol tiglate.

Initial data collected			
Patient number	149	Tumor number	151
Breed	149	Information regarding previous treatments	151
Sex/neuter status	149	Location of mast cell tumor on body	151
Weight	149	Cutaneous versus subcutaneous	151
Staging information	149	If sedation was used	151
Age	148	Dose of tigilanol tiglate (mL)	148
		Tumor longest diameter	146
		Tumor volume	145
		Histologic grading	22
		Cytologic grading	17
Data available at 1 month			
Patient number	117	Tumor number	119
		Information regarding concurrent treatments	119
		Response rate	113
		Wound healing time	90
		Wound size	67
Data available at 1 year			
Patient number	86	Tumor number	88
		Response rate	88

86 treatments; 3 treatments required general anesthesia; and 62 treatments did not require sedation or anesthesia. Additional data about each MCT treatment at enrollment is presented in Table 2.

Various 1 month follow-up data was available for 119 treatments, including response in 113 treatments (Table 4). Eighty-five treatments of 113 (75%) tumors resulted in a CR after 1 injection of tigilanol tiglate. Of 28 treatments that did not result in a CR at 1 month, 22 tumors were retreated (79%) with 68% of those achieving a CR after the 2nd dose (13/19; Table 5). When available, data about wound formation was collected (n = 67). Median wound area was 4.71 cm^2 (range, 0.09-100 cm^2); median time to largest wound formation was 7 days (range, 1-91 days). The wound took a median of 30 days to heal completely (range, 14-154 days; n = 90). Additional MCTs developed at distant sites (not considered recurrence of the primary tumor) in 16 dogs.

The fractional polynomial regression best fit curve evaluating the correlation between tumor volume and wound size was found to be as follows: wound area = 4.6582(tumor volume)$^{0.6251}$ (Figure 2). A 2nd plot of wound area square root versus tumor volume cube root along with corresponding linear regression was computed. For these data (Pearson) correlation coefficient was $R = 0.64$ with an R^2 of 0.40, meaning approximately 40% of the variance in square root wound area can be attributed to changes in cube root of tumor volume

TABLE 2 Data about mast cell tumors treated with intratumoral tigilanol tiglate.

	Number of tumors
Anatomic location	(n = 151 tumors)
Limb	101 (67%)
Other	25 (17%)
Trunk	14 (9%)
Muzzle	8 (5%)
Mucocutaneous junction	3 (2%)
Type of MCT	(n = 151 tumors)
Cutaneous	107 (71%)
Subcutaneous	44 (29%)
Diagnosis	(n = 151 tumors)
Cytology	127 (84%) [17 were cytologically graded]
Low grade	17
High grade	0
Histopathology	22 (15%)[a]
Patnaik grade 1	0
Patnaik grade 2	16
Patnaik grade 3	0
Kiupel low grade	12
Kiupel high grade	5
Staging	(n = 96 patients had some form of staging)
Regional lymph node aspirates	44 (46%)
Abdominal ultrasound	65 (68%)
Aspirates of the spleen, liver, or both	42 (44%)
Chest radiographs	42 (44%)
Other	6 (6%; most commonly reported as CBC and chemistry profile)
Metastatic disease identified	6/96 (6% for all patients staged; 14% [6/44]of regional lymph nodes)
Regional lymph node	6
Treatment before tigilanol tiglate	(n = 151 tumors)
None	122 (81%)
Surgery	17 (11%)
Steroids	8 (5%)
Chemotherapy	6 (4%)
Vinblastine	4
Toceranib phosphate	3
CCNU/Lomustine	1
Other not specified	1
Immunotherapy	2 (1%)
Electrochemotherapy	1 (0.7%)
Radiation therapy	0

[a]Histologically, 5 mast cell tumors were graded based on the Kiupel scheme only; 6 were graded based on the Patnaik scheme only; 11 were graded based on both the Patnaik and Kiupel schemes.

TABLE 3 Concurrent medications administered with intratumoral tigilanol tiglate.

Medication	Number of mast cell tumor tigilanol tiglate treatments that received the concurrent medication (n = 119)
Antidiarrheal	6 (5%)
Antiemetic	2 (1.6%)
Appetite stimulant	0
H1 blocker	108 (91%)
H2 blocker	107 (90%)
Other	14 (12%; most commonly antibiotics and supportive medications for unrelated comorbidities)
Pain medication	91 (76%)
Amantadine	1
Gabapentin	81
Tramadol	21
Other	6
Proton pump inhibitor	8 (7%)
Corticosteroids (PO or injectable)	112 (94%)

TABLE 4 Response data 1 month after intratumoral treatment of mast cell tumors in dogs using tigilanol tiglate.

Response to treatment at 1 month (n = 113[a])	
Complete response	85 (75%)
Partial response	22 (19%)
Stable disease	4 (3%)
Progressive disease	2 (2%)

[a]Data not available for 38 treatments.

TABLE 5 Response data after retreatment with tigilanol tiglate.

Response to 2nd tigilanol tiglate treatment (n = 19[a])	
Complete response	13 (68%)
Partial response	3 (16%)
Stable disease	1 (5%)
Progressive disease	2 (11%)

[a]Twenty-two patients were retreated, but data was not available for 2 patients and 1 patient was euthanized after retreatment.

(Figure 3). This indicates a moderate correlation between wound area and tumor volume.

Data for 88 treatments were available at 1 year after intratumoral tigilanol tiglate. Fifty-six MCTs (64%) achieved a durable CR at 1 year after a single treatment (Table 6). Eighteen of 88 MCTs (20%) were retreated 1 month after the initial treatment because of only a partial remission or progressive disease or regrowth of the primary tumor. Five of these 18 achieved a CR after the 2nd dose. In total, 61/88

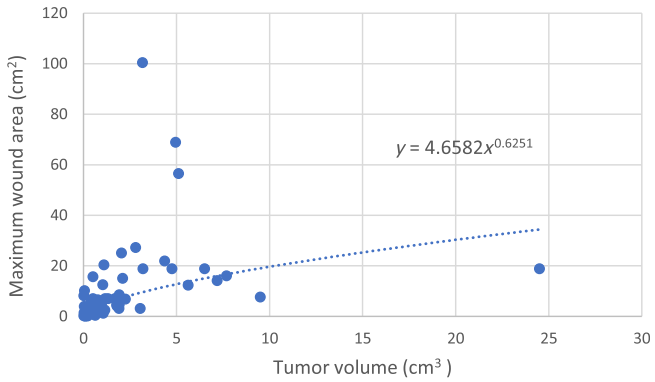

FIGURE 2 Fractional polynomial regression best fit curve evaluating the correlation between tumor volume (cm^3) and wound area (cm^2).

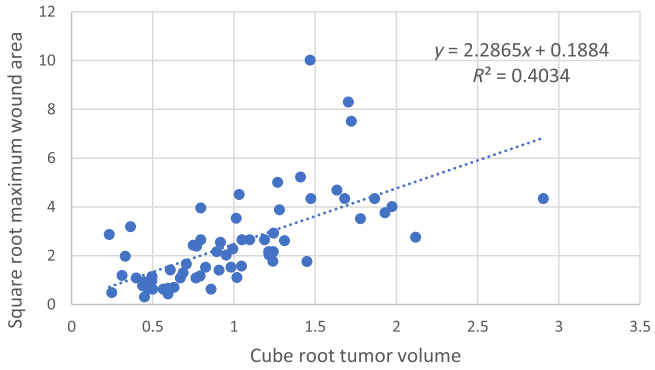

FIGURE 3 Linear regression relationship between square root wound area versus cube root tumor volume. A moderate correlation between wound area and tumor volume exists.

TABLE 6 Response data 1 year after intratumoral treatment using tigilanol tiglate.

Response to treatment at 1 year (n = 88)	
Complete response after 1 dose	56 (64%)
Complete response after 2 doses	5 (6%)
Partial response	7 (8%)
Stable disease	5 (6%)
Progressive disease	15 (17%)

(69%) MCTs achieved CR that was durable at 1 year after 1 or 2 treatments with tigilanol tiglate.

4 | DISCUSSION

Tigilanol tiglate is a novel intratumoral treatment approved for non-metastatic cutaneous MCTs in dogs, and nonmetastatic SC MCTs located at or distal to the elbow or hock, that are <10 cm^3.[9] We found that in a population of patients presented to veterinary oncologists, the CR rate for tigilanol tiglate at 1 month was 75% (n = 85/113) with 64% of patients evaluable (n = 88; 56/88) maintaining this response for at least 1 year after 1 dose of tigilanol tiglate. These data, the largest set thus far with 1 year of follow-up, supports the consideration of using tigilanol tiglate for local treatment of MCTs in dogs and are consistent with results from the controlled trial.

The initial clinical study evaluating tigilanol tiglate found that 75% of MCT patients experienced CR by day 28.[12] The study was a controlled, randomized, masked trial in which patients enrolled were limited to those with stage Ia or IIIa MCTs according to the World Health Organization staging scheme,[19] thus excluding patients with known or suspected metastatic disease.[12] Additional exclusion criteria included patients that had received anticancer treatment within the previous 2 months, and tumors that were >10 cm^3 or <1 cm in diameter.[12] We had expected that if data were collected from a more diverse population of patients, the reported CR rate would decrease. However, our study, which included patients from a population that had received previous anticancer treatment, patients with evidence of local metastasis, and tumors that ranged in size from 0.4 to 6.2 cm in longest diameter, had an identical CR rate of 75%.

Although the patient population in our study is more diverse when compared with the 1st trial, the tumor characteristics (median tumor diameter and volume) are similar. In general, most of the tumors treated were relatively small. This factor may be bias introduced by oncologists selecting patients for tigilanol tiglate with tumors that were more likely to respond well and less likely to have complications after treatment.

Extrapolating the CR rate reported here and in the initial trial to biologically more aggressive or high-grade tumors may be flawed. First, both studies reported a low number of tumors in anatomical areas known to harbor more aggressive tumors (muzzle and mucocutaneous junctions).[20,21] Second, patient tumors in the initial trial were graded using the Scarpa system of cytologic grading resulting in 11% of patients diagnosed as high grade.[22] In our retrospective survey, cytologic tumor grade was not required for data entry and was known in a relatively low number of reported cases (13%) with 0% determined as high grade (Table 2). Given the lack of known high-grade tumors in our study, we cannot infer what CR rate would be expected in dogs with high-grade tumors. A small study of 18 patients with cytologically high-grade MCTs reported a CR rate at 28 days of 44% for those treated with a single injection of tigilanol tiglate, and thus a less robust response might be expected for high-grade tumors.[14]

The signalment of the patients described in our study are consistent with previous reports of MCTs in dogs: brachycephalic breeds and Labradors were over-represented,[23-25] and patients tended to be older.[26] The majority of tumors treated were considered to be cutaneous, and most were located on the limb or trunk, as previously reported.[27-30] For patients that underwent any form of staging, the most common metastatic site was the regional lymph node, found to be positive in 14% of patients evaluated (6/44). This finding is in contrast to previous studies where lymph node metastasis has been reported to be higher.[31] However, the likelihood of a high population of low-grade tumors in our cohort may have biased this finding. In

addition, not all patients were staged before treatment, and thus, metastatic disease may have been missed.

Historically, a lack of consensus exists among oncologists regarding diagnostic criteria and clinical staging for MCT in dogs. A Working Congress met in 2019 to better define both diagnostic criteria and classification of MCT in dogs.[32] The proposed consensus established that adequate clinical staging for MCTs should include a complete physical examination, blood tests (CBC and biochemistry panel), evaluation of the regional, or ideally, sentinel lymph node by fine needle aspirates, abdominal ultrasonography (with fine needle aspiration of the spleen and liver) and thoracic radiographs.[32] With this definition, most patients included in our study would not be considered fully staged. Even with lymph node fine needle aspiration, a proportion of lymph nodes with metastasis may be missed and lymph node extirpation is now recommended to accurately assess disease stage.[33] In addition, it is notoriously difficult to determine which lymph node will be the sentinel lymph node in dogs with MCTs. Indeed, the sentinel and regional lymph nodes differ in 28% to 63% of cases.[34] Lymph node mapping was not completed in this group of patients, and thus it is possible that the lack of lymph node metastasis identified was simply because of inaccurate identification and sampling of the sentinel lymph node.

The current label indication for tigilanol tiglate limits use to patients with nonmetastatic MCTs and, to our knowledge, its safety and efficacy in MCT patients with metastatic disease has not been evaluated. The wounds of the patients treated in the 1st clinical study were analyzed in detail and published in a subsequent study.[18] The investigators concluded that patients with enlarged pretreatment regional lymph nodes tended to develop larger and more variable-sized wounds. Although pretreatment screening by fine needle aspirate confirmed no metastatic disease in these enlarged nodes, pathologist comments made it clear that sampling was of moderate to good cellularity in half of the cases, leaving definitive assessment of metastasis lacking. Furthermore, clear suspicion of MCT in the lymph node was present in 33% (4/12) of the cases. Local lymph node enlargement, caused either by metastasis or inflammation, may disrupt lymphatic flow and impede drainage of edema fluid caused by tigilanol tiglate from the treatment area, potentially leading to larger wound formation.[18] Unfortunately, wound size information in our patient subset was only available for 2/6 treated cases with known lymph node metastasis. However, those 2 treatments resulted in wounds that were well-above the median (7.6 and 100 cm^2; median, 4.71 cm^2), 1 of which was the upper bound of the range (100 cm^2).

The current FDA label limits treatable tumor volume to <10 cm^3. This recommendation is consistent with the available safety and efficacy data. Larger tumors may be more at risk for extensive wound formation or undertreatment of the tumor.[12] Three patients in the current cohort had tumor volume >10 cm^3. Only 1 of these patients had wound size reported, and it was well-above the median at 18.8 cm^2. The decision to treat patients with tumors >10 cm^3 or known lymph node metastasis in this data set was at the discretion of the attending clinician (these 2 groups did not overlap). Based on published data, avoiding tigilanol tiglate in patients with large tumor size and known metastatic disease is recommended.

After intralesional administration, tigilanol tiglate's mode of action leads to mitochondrial swelling, plasma membrane destruction, and activation of protein kinase C, increasing tumor vasculature endothelial permeability, and leading to hemorrhagic necrosis and tumor cell death.[8] Thus, wound formation is a distinguishing and expected feature of treatment. The volume of the treated tumor has been shown to moderately correlate with wound size,[18] which also was confirmed in our study. Previously, complete healing was reported to occur in most patients between 28 and 42 days,[18] and wound healing intervention was limited to 4% (5/117). In our cohort, the median wound area was 4.71 cm^2 with a median time to largest wound formation of 7 days. The wounds took a median of 30 days to heal completely, consistent with previous studies.[18] In comparison, wound healing after 1st intention wound closure takes on average 7 days.[35] Although the wound healing after tigilanol tiglate treatment is prolonged in comparison, the wounds post-tigilanol tiglate heal rapidly by secondary intention after tumor slough and generally require minimal intervention.[12,18] The difference in post-treatment wound healing time should be discussed with owners before proceeding with treatment.

Treatment with tigilanol tiglate generally precludes histologic evaluation of MCT grade. Historically, grade has been 1 of the most relied upon prognostic factors for predicting MCT behavior in dogs.[36] Although a cytologic grading scheme has been adopted, it has not been shown universally to be predictive of MCT behavior and outcome.[22,37] Thus, an important potential consideration when using tigilanol tiglate is the lack of histologic grading and prognostic information. Tissue biopsy to obtain grade and prognostic information may be done before tigilanol tiglate treatment, but given the intratumoral administration, there is a risk of leakage or loss of the drug through the biopsy site that could lead to a decrease in efficacy and an increase in exposure to those coming in contact with the patient. After biopsy, tigilanol tiglate treatment should be delayed until the biopsy site is fully healed. This recommendation could result in delayed local tumor control.

It has also been reported that tigilanol tiglate can be injected intratumorally without the need for anesthesia or sedation.[12] In our study, only 3 treatments required general anesthesia and 86 required sedation. This observation confirms that sedation is not required for this treatment, potentially expanding the population of patients that can receive local treatment for MCTs if age or comorbidities preclude the use of anesthesia or sedation.

To decrease the potential effects of local or systemic degranulation after intralesional tigilanol tiglate, H1 and H2 antagonists and corticosteroids are recommended before treatment.[12] The majority of patients (90-94%) in our survey received 1 or all of the recommended pretreatment medications. Why some patients did not receive these medications was not captured. Although the use of corticosteroids before tigilanol tiglate may help to decrease adverse effects, it could impact the response evaluation or the ability to treat the MCT if a robust response to the corticosteroid alone is observed. Indeed, data for 1 patient was excluded from analysis because it was discovered that an adjacent lipoma (diagnosed by cytology) was treated instead of the intended MCT after the MCT resolved with corticosteroids

alone. The treated lipoma developed the expected local bruising, edema, and discomfort, but no wound formed. Ultimately, the lipoma did not resolve after tigilanol tiglate treatment.

Because of tigilanol tiglate's mode of action, local treatment pain is a common adverse event after tigilanol tiglate injection.[12] Seventy-six percent of patients in our cohort received at least 1 pain medication after the procedure. Although not evaluated in our study, in previous reports the median duration for pain medication use after tigilanol tiglate injection was 6 days, with an average of 9 days.[12] The recommended duration of analgesia after surgery or tigilanol tiglate treatment is variable and depends on the individual patient, treatment location and procedure.[38] As with other treatments intended for local tumor control, preemptive analgesia is recommended with tigilanol tiglate treatment.[39] Other supportive medications typically associated with chemotherapy use such as antidiarrheals, antiemetics, and appetite stimulants were used infrequently (Table 3).

The success of surgical intervention for local tumor control of MCTs is high. The recurrence rate for low-grade MCTs, even without achieving clean histologic margins (>1 mm), is very low; 1 study reported that no patients had local recurrence at the site of initial surgery for a median of 976 days.[4] This observation is in comparison to an 89% CR rate at 1 year after a single tigilanol tiglate treatment for those patients that initially achieved CR.[13]

In our cohort, 64% of patients with 1 year follow-up available had a durable CR after 1 injection of tigilanol tiglate. This percentage is a decrease compared with the study evaluating recurrence at 6 and 12 months after tigilanol tiglate injection where 89% of patients remained tumor-free at 12 months.[13] The former study had data retrospectively retrieved from the efficacy trial that was well-controlled. This finding suggests that, in a more diverse population, durable responses may be less likely, but are still relatively robust.

In keeping with pharmacological vigilance and regulatory standards, all adverse events observed by oncologists entering data were reported to Virbac directly. It was elected not to capture adverse events associated with treatments. This decision was made for 2 reasons: (1) at the time of data capture, tigilanol tiglate recently had been approved by the FDA, and in accordance with pharmacological vigilance and regulatory standards, veterinarians were directed to contact Virbac with concerns because data capture was not being monitored in real time and (2) expected adverse events had already been well-documented in the published literature.[8,11,12]

Despite the numbers and diversity of patients, our study had some limitations. Treated MCTs were not all graded, and clinical staging was not required or standardized. Additionally, the identification of cutaneous versus SC tumors was made clinically. This practice often is used to describe MCTs before treatment but is not necessarily a sound basis for determining biological behavior or prognosis. Technically, classification of a SC MCT is based on histopathologic involvement of the SC structures and not the dermis.[32] This may lead to misinterpretation of the results, because the true biologic behavior of the MCT is unknown.

Retrospective studies also carry a substantial chance of bias. The data presented here are based on surveys typically completed after treatment commenced. This practice increases the chance of recall bias and may skew the results if the patient population reported contains more, or fewer, favorable patients that may be remembered by the contributing clinician. In addition, only 6% of the potential population of ACVIM-board certified oncologists replied to the request for cases. This low percentage could have biased the results toward cases seen by those individuals who may be particularly interested in research or amenable to the use of tigilanol tiglate, potentially limiting the ability to expand the findings reported here to a broader population of patients. However, it is unknown how many of the 607 board certified oncologists use tigilanol tiglate. Thus, although only 6% responded, that percentage may be erroneously low if <607 use tigilanol tiglate in their practice.

The data reported here provide information about the largest cohort of canine MCT patients treated with tigilanol tiglate and followed to 1 year post-treatment. The previously reported response data was confirmed in an even more diverse patient population. However, considering the decrease in CR at the 1-year follow-up in a clinical setting compared to the initial study, careful consideration and client education is needed before choosing tigilanol tiglate over surgery for local control of MCTs, especially if the tumors do not fulfill the FDA label indication.

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CONFLICT OF INTEREST DECLARATION

Margaret Musser has received financial support from QBiotics Group Ltd. Chad M. Johannes is a paid consultant and speaker for QBiotics Group Ltd. P.D. Jones is an employee of QBiotics Group Ltd. No other authors declare a conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

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

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

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

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