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Comparative Efficacy and Safety of Two Treatment Regimens with a Topically Applied Combination of Imidacloprid and Moxidectin (Advocate®) against Generalised Demodicosis in Dogs

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Abstract

This laboratory study compared the efficacy of two treatment regimens using an imidacloprid (10%) /moxidectin (2.5%) topical formulation (Advocate®, Bayer) on dogs with generalised demodicosis. Sixteen dogs were randomly allocated to two equal groups. One group was treated at 28-day intervals for 12 weeks and the second group at weekly intervals for 15 weeks. Mite numbers were estimated and demodectic lesions were evaluated on each dog before treatment and at approximately 28-day intervals thereafter. Consistently greater reduction in mite numbers was recorded for the weekly treatment regimen. Dogs treated at weekly intervals exhibited markedly fewer clinical signs and greater hair regrowth and weight gain than those treated at 28-day intervals. To assess the safety of a weekly treatment interval in dogs, a study was done in which the investigational compound was administered at weekly intervals at five times the recommended dose for a period of 16 consecutive weeks. Apart from transient erythema at the site of administration in one dog and scaliness of the skin in another, no clinical signs of toxicity could be observed. Assessment of 27 blood parameters indicated that only basophils were outside the reference values on days +13 and +69, during the safety trial period.

Introduction

Zumpt (1961), in his monograph on the mites infesting vertebrates in sub-Saharan Africa, states that *Demodex* is the only genus encountered in the family Demodicidae, and lists five species that had been recorded in this region at that time. He also asserted that many more species would certainly be present, and that *D. canis* in some races of dogs gives rise to very severe pathological reactions which, when complicated by a bacterial infection, may even lead to death. Shipstone (2000) mentions that three species of *Demodex* mites have been reported on dogs and that although all three have been implicated in the aetiology of demodectic mange, *D. canis* is the most common cause of this disease.

Small numbers of *Demodex* spp. mites constitute a normal component of the dog's cutaneous fauna and with the exception of the initial transfer of mites from bitches to their pups during nursing in the first few days of their lives, infestation is not considered to be contagious. However, under certain predisposing conditions, of which immunosuppressive disease conditions are probably one of the most common, a marked proliferation in mite numbers in hair follicles and in the pilosebaceous glands occurs. This increase in mite numbers (Fig. 1) and the pathology of the dermis that accompanies it is known as demodectic mange, and may present in severe forms in dogs.

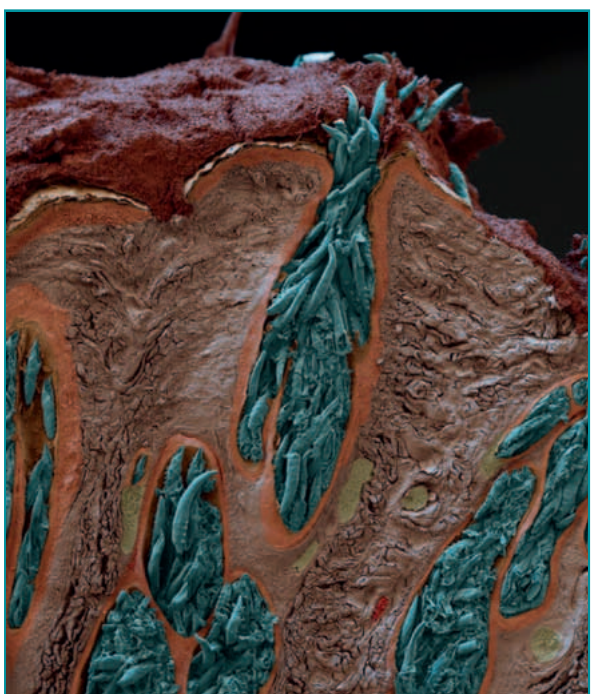

Fig. 1 *Demodex* spp. mites in hair follicles of a dog (SEM, coloured)

Depending on the extent of the lesions demodectic mange in dogs is classified as localised or generalised. The localised manifestation usually occurs in young dogs (< 2 years old) and is characterised by discrete patches of alopecia and erythema and generally resolves spontaneously (Paradis 1999). Generalised demodectic mange may develop from the localised condition or occur in older animals, in which it is often associated with an immunosuppressive disease (Shipstone 2000). However, some authors believe that immunosuppression is induced by the parasite, or the host's reaction to it, and that it therefore follows rather than precedes the clinical manifestation of generalised demodicosis (Barriga et al. 1992). Demodectic mange is regarded as generalised if localised disease is present at five or more sites on the skin surface, or if an entire body region is affected, or if two or more feet, a condition known as pododemodicosis, are affected (Shipstone 2000). If the disease has persisted for at least 6 months, it can be regarded as chronic generalised demodicosis (Paradis and Page 1998).

Currently available therapeutic options to treat generalised demodicosis entail daily, weekly, fortnightly or monthly treatments for periods of 2 months or more (Medleau and Willemse 1995; Miller et al. 1995; Paradis 1999; Wagner and Wendlberger 2000; Mueller 2004; Fourie et al. 2007). Because the mode of administration of some of the compounds is labour-intensive, and often time-consuming, their application may be associated with premature cessation of therapy (Paradis 1999). In reviewing different treatment protocols for demodicosis, Mueller (2004) concluded that there is good evidence for recommending daily oral treatment with moxidectin (400 μg kg^{-1}). Such a treatment is not approved by

regulatory authorities, and although rare, possible severe adverse effects of macrocyclic lactones have been reported (Mueller 2004).

An imidacloprid (10%)/moxidectin (2.5%) spot-on (Advocate®), applied at monthly intervals, has previously been shown to control *Demodex* spp. mites on dogs (Fourie and Heine 2005; Heine et al. 2005). However, in severe cases of demodicosis, the resolution of clinical symptoms in animals treated at monthly intervals may be slow. In order to address this situation, a study was designed to compare weekly and monthly administrations of Advocate® to dogs suffering from generalised demodicosis and to compare reduction in mite numbers and resolution of clinical signs between the two treatment regimens. The safety of weekly administrations was also ascertained.

Materials and methods

The studies were performed in compliance with recognised quality standards at the facilities of ClinVet International, Bloemfontein, South Africa. The therapeutic efficacy study was performed according to Good Clinical Practice (GCP-GL9 2000), and the safety study in compliance with the OECD principles of Good Laboratory Practice.

Therapeutic efficacy assessments

Ten male and six female crossbred dogs, older than 1 year, were used in the study. All the animals presented with signs of generalised demodectic mange, and skin scrapings taken from each dog were positive for *Demodex* spp. mites. With the exception of clinical signs associated with chronic generalised demodicosis, the dogs were otherwise healthy on veterinary assessment on day –1 and weighed between 6.28 and 23.09 kg, and the bitches were not pregnant.

Each dog was fitted with an electronic transponder with a unique alphanumeric code and was housed individually in an indoor/outdoor run that conformed to accepted animal welfare guidelines, and no contact between animals was possible. The animals were acclimatised to the study conditions for at least 28 days prior to initial treatment with the investigational veterinary product. On day –28, a skin biopsy was taken under anaesthetic from every dog. Thereafter each animal was treated twice daily for 6 weeks with cefalexin at 20–30 mg/kg body weight to counteract secondary bacterial infection associated with infestation, and concurrently fed brewers yeast to support its intestinal flora. A second biopsy was taken on day +13 and if no bacteria or inflammatory cells were encountered, antimicrobial therapy was discontinued. If there was evidence of active infection, but with fewer inflammatory cells and/or bacteria compared to the first biopsy, treatment with cefalexin was continued for a further 4 weeks. If, however, clinical and cytological deterioration was detected on day +13, antibacterial therapy was continued with enrofloxacin at 5 mg/kg body weight for 4 to 6 weeks. All dogs were observed at least once daily for general signs of healthiness for the duration of the study.

The investigation was conducted in two groups of dogs, each consisting of eight treated animals. Animal welfare considerations and the already chronically diseased condition of the animals made it inadvisable to include an untreated control group. The dogs were ranked on their day –1 body weights and randomly allocated within gender to the two treatment groups. They were treated with a commercial formulation of imidacloprid (10%) and moxidectin (2.5%) (Advocate®) at a dose rate of 1 ml for dogs weighing >4–10 kg and 2.5 ml for those >10–25 kg as recommended by the manufacturer. When, during the course of the study, the weight of individual dogs increased to above 10 kg, their dose volume was adjusted accordingly. Doses were calculated using pre treatment body weights and were applied to healthy skin as a single spot between the shoulder blades. The animals in group 1 were treated a maximum of four times at 28-day intervals and group 2 a maximum of 16 times at 7-day intervals starting on day 0. When two successive mite counts for a particular dog in group 1 were negative, its

treatment was discontinued, provided it had received at least two treatments, and if it was in group 2, provided that it had received at least eight treatments.

Deep skin scrapings (~ 4 cm^2) were taken from five sites near comedones or expanding lesions on each animal on days –28, –2, +27 and at 28-day intervals thereafter until day +168/9 in order to assess mite infestations. The original sites scraped were recorded and these sites and/or new lesions were scraped at each subsequent examination. Each scraping was transferred to a labelled microscope slide containing mineral oil and was examined under a stereomicroscope for the presence of live *Demodex* spp. mites. The number of mites (immature and adult live mites combined) that was counted in each scraping was recorded separately.

Clinical signs of infestation and the extent of demodectic lesions on each dog were assessed on the days when scrapings were made. The following parameters were assessed for each dog and sketched on a silhouette of the left and right hand side of a dog: body areas covered by casts, scales and crusts; body areas with hair loss (on a scale of 1 = slight thinning to 3 = no hair); and body areas with erythema. The animals were also comprehensively photographed on day –2 and at approximately monthly intervals thereafter until day +168/9.

Descriptive statistics were used to portray the number of mites present on each assessment day and the percentage change in mite counts from day –2 (baseline). A one-sided assessment for superiority (Wilcoxon-Mann-Whitney test) was employed to differentiate between the mite counts recorded for the two treatment regimens on the various assessment days. Efficacy, based on a reduction in the geometric mean (GM) numbers of mites (live immatures and adults combined) relative to pre treatment numbers, was calculated as follows:

$$\% \text{ eff.} = \frac{(\text{GM pre treatm. count} - \text{GM post treatm. count})}{\text{GM pre treatm. count}} \times 100$$

Data on skin lesions, namely casts, scales, crusts, hair loss and erythema, were summarised and tabulated for each dog, as it were the overall changes in clinical appearance by a comparison of pre and post treatment digital images. A semi-quantitative assessment of hair regrowth was also made and a score relative to pre treatment values was awarded to each dog on the various post treatment days. A score of 1 = body areas with hair regrowth of 0–50 % compared to that recorded in the pre treatment assessment; 2 = hair regrowth > 50 % and < 90 % compared to that recorded originally; and 3 = hair regrowth > 90 % compared to that recorded originally.

Safety assessments

Twelve healthy crossbred dogs, acclimatised to the study facility for seven days and weighing between 7.46 and 18.32 kg were used in the study. The dogs were ranked according to body weight, which was the only criterion used when they were allocated to two groups consisting of eight (group 1) and four (group 2) animals by randomisation through minimisation. Group-1 dogs were treated once a week for 17 consecutive weeks, starting on day 0, with Advocate® at a dose volume of 0.5 ml per kg body weight. This is equivalent to five times the recommended minimum dose. The medicament was applied directly to the skin between the shoulder blades. Group-2 dogs served as untreated controls. The dogs were housed indoors in individual kennels with full environmental control.

Venous blood for chemical and haematological analysis was collected from each dog on day –1 and day +6, and subsequently on a weekly basis. The parameters which were measured are shown in Table 1.

Following each treatment, detailed observations of wellness were made on each dog for four hours and subsequently twice a day for two days. General health observations were made on the dogs on all the intervening days. Clinical examinations were also performed on all dogs on days –7, –1, +27, +55, +83 and +111. Body weights were recorded on day

Table 1 Chemical and haematological blood parameters recorded at regular intervals during safety assesment study

Clinical Chemistry	Haematology
Total Serum Protein (TSP) g/l	Red cell count
Albumin g/l	Haemoglobin
Globulin g/l	Haematocrit
Urea mmol/l	Mean corpuscular volume (MCV)
Creatinine µmol/l	Mean corpuscular haemoglobin (MCH)
ALP (Alkaline phosphatase) units/l	Mean corpuscular haemoglobin concentration (MCHC)
AST (Aspartate aminotransferase) units/l	White blood cell count
ALT (Alanine aminotransferase) units/l	White blood cell differential count
Amylase units/l	Platelet count
Glucose mmol/l	
Sodium mmol/l	
Chloride mmol/l	
Potassium mmol/l	
Phosphorus (SIP) mmol/l	
Calcium (total) mmol/l	
Total bilirubin µmol/l	
Direct bilirubin µmol/l	
LDH (lactic dehydrogenase) units/l	

–1 and then monthly until day +111. Using a scoring system, the amount of food consumed daily was recorded.

Statistical analysis focused on the change from baseline values in each of the haematological and clinical chemistry parameters. The extent, and specifically the relevance of such changes from a clinical point of view, were evaluated and interpreted descriptively. Two reference ranges were used, namely reference range 1, which comprised the minimum and maximum values of pre treatment parameters across all groups on day –1, and reference range 2, as provided by the laboratory (Pathcare Veterinary Laboratory, Bloemfontein) responsible for the pathology. The number of post treatment values that fell outside these reference ranges was calculated and summarised in tables.

Post treatment values were compared to baseline values in a within-treatment comparison by means of an ANOVA with an animal and observation time (baseline, post treatment) as effects. A between-treatment comparison in respect of changes from the baseline was also performed by means of an ANOVA with a treatment effect.

The biological relevance of changes was considered cardinal. Statistical methods were used as aids to evaluate the results, but statistical significance was not the determining factor.

Results

Therapeutic efficacy assessments

The efficacy of the two treatment regimens against *Demodex* spp. mites is compared in Table 2. The efficacy of 7-day interval treatments with the spot-on formulation of imidacloprid and moxidectin was consistently greater than that of 28-day interval treatments with the same formulation, and was statistically superior on days +27, +83 and +111 of assessment (Wilcoxon-Mann-Whitney).

From day +55 onwards the reduction in the frequency of occurrence of erythema compared to pre treatment levels was always greater in the dogs treated at 7-day intervals than in those treated at 28-day intervals (Table 3). The frequency of occurrence of crusts, casts or scales remained between 87.5% and 100% in the dogs treated at 28-day intervals, where-

Table 2 Comparative efficacy of a spot-on formulation of imidacloprid and moxidectin administered at 28-day or at 7-day intervals against *Demodex* spp. on dogs

Days pre or post treatment	Group 1: 28-day treatment intervals		Group 2: 7-day treatment intervals	
	Geometric mean mite count	Efficacy (%)	Geometric mean mite count	Efficacy (%)
–2	221.7	–	423.7	–
+27	144.9	34.6	17.0	96.0[a]
+55	29.5	86.7	1.3	99.7
+83	67.2	69.7	2.6	99.4[a]
+111	4.3	98.0	1.7	99.6[a]
+139	41.6	81.2	17.7	95.8
+168/9	31.2	85.9	11.0	97.4

[a] efficacy superior (Wilcoxon-Mann-Whitney)

Table 3 Comparative reduction in skin lesions and increase in body weight of dogs treated at 28-day (group 1) or at 7-day (group 2) intervals with a spot-on formulation of imidacloprid and moxidectin against *Demodex* spp.

Days pre or post treatment	Frequency of occurrence				Mean body weight (kg)[a]	
	Erythema		Crusts, casts or scales			
	Group 1 (n = 8)	Group 2 (n = 8)	Group 1 (n = 8)	Group 2 (n = 8)	Group 1 (n = 8)	Group 2 (n = 8)
–2	8	5	8	8	12.99	12.89
+27	4	3	8	8	14.50	14.71
+55	5	1	8	8	15.23	15.87
+83	6	1	8	7	15.37	16.04
+111	6	1	7	7	14.86	15.99
+139	5	2	8	5	15.09	16.43
+168/9	3	1	7	3	15.15	16.93

[a] measured on day –1, +27, +55, +83, +104, +126 and +168/9

Table 4 Comparative hair regrowth on dogs treated at 28-day or at 7-day intervals with a spot-on formulation of imidacloprid and moxidectin against *Demodex* spp.

Days post treatment	Hair regrowth score: frequency of occurrence					
	Group 1 (n = 8): 28-day treatment intervals			Group 2 (n = 8): 7-day treatment intervals		
	1 (0–50 %)	2 (50–90 %)	3 (>90 %)	1 (0–50 %)	2 (50–90 %)	3 (>90 %)
27	4	2	2	3	4	1
55	4	2	2	1	3	4
83	6	1	1	2	1	5
11	6	1	1	1	1	6
139	5	2	1	1	1	6
168	4	2	2	1	1	6

as it showed a steady decline from 100 % on day +55 after treatment to 37.5 % at the conclusion of the study on day +168/9 (Table 3). Only two of the eight dogs treated at 28-day intervals exhibited hair regrowth in excess of 90 % of their initial hair cover compared to six of the eight dogs treated at 7-day intervals (Table 4). The improvement in skin lesions associated with generalised demodicosis was accompanied by a gain in body weight in both groups of dogs. The mean body weights of the two study groups were closely similar on day –2, however, the dogs treated at 28-day intervals gained an average of 2.16 kg compared to 4.04 kg for the dogs treated at 7-day intervals (Table 3).

Safety assessments

During the specific health observations, one dog (group 1) – at different times after the first nine applications – displayed erythema at the site of application. No erythema was recorded from the tenth application onwards. Another dog displayed slight scaliness at the application site on days +28, +35 and +42. Emesis by two dogs in group 1 was recorded on two occasions. In general, food consumption was normal, and this was accompanied by an increase in mean body weight from 13.24 kg on day –1 to 14.46 kg on day +111 in group 1, and from 12.79 kg to 12.87 kg in group 2.

Comparisons *within* groups indicated that in most cases, the post treatment values in that particular group with respect to the various blood constituents remained within the reference ranges. The statistically significant ($p < 0.05$) changes from baseline, and of which the mean post treatment values of that particular treatment group were outside the reference ranges on specified days, are summarised in Table 5. Comparisons *between* groups indicated that in most cases where the difference between groups with respect to the change from baseline were statistically significant, the post treatment means nevertheless remained within the reference ranges. The *between*-group differences with respect to the change from baseline that were statistically significant ($p < 0.05$) and of which either of the post treatment group means were outside the reference ranges are summarised in Table 6.

Discussion

The protocol for the present study was based on that of two previous efficacy studies in dogs with

Table 5 *Within* group comparison of dogs either treated at a 7-day interval with a spot-on formulation of imidacloprid and moxidectin (group 1) or untreated (group 2): significant ($p < 0.05$) changes from baseline within a specific treatment group, and of which the post treatment mean values were outside the two reference ranges

Haematology parameters	Study day	High/Low (in relation to reference range)	Relevant group
Basophils	Day +13 Day +69	High High	1
MCHC	Day +41[a]	High	1
Clinical chemistry parameters[a]	**Study day**	**High/Low (in relation to reference range)**	**Relevant group**
Sodium	Day +41[a]	High	1
Total protein	Day +55[a] Day +69[a]	Low Low	1
Globulin	Day +48 Day +62[a]	Low Low	1
Albumin/Globulin ratio	Day +48[a] Day +62[a]	High High	1
Urea	Day +97[a]	High	2
Calcium	Day +83[a]	Low	2

[a] outside ref range 1, but still within ref range 2

Table 6 *Between* group comparison of dogs either treated at a 7-day interval with a spot-on formulation of imidacloprid and moxidectin (group 1) or untreated (group 2): significant difference between groups with respect to the change from baseline and of which either of the post treatment group means were outside the reference ranges

Clinical chemistry parameters[a]	Study day	High/Low (in relation to reference range)	Relevant group
Chloride	Day +41	Low	2
Albumin/Globulin ratio	Day +48[c]	High	1
Urea[b]	Day +76 Day +90 Day +97	High High High	2 2 2

[a] LDH not judged as no reference range was available
[b] one dog in the group had high levels of creatinine and urea from day +13 causing a higher mean value. This may indicate a kidney disorder in the one dog. It had no outward sign of disease however
[c] outside reference range 1 but still within reference range 2

generalised demodicosis, to which the imidacloprid/moxidectin spot-on combination was applied at 28-day intervals. One of these was a field study conducted at veterinary practices in Europe in which no mites could be detected at the end of the investigation in 26 of 30 treated dogs (Heine et al. 2005). The other was a laboratory study in which a geometric mean reduction in mite numbers of 98% was achieved, but 14 of 18 treated dogs still had mite counts at the conclusion of the study (Fourie and Heine 2005). Despite the presence of mites, the majority of dogs in both studies displayed a marked improvement in clinical signs.

The present study partially repeated the protocol of the previous two studies in that a group of dogs treated at 28-day intervals was included, but in an attempt to improve efficacy, a second group of dogs was treated at 7-day intervals. The results indicate that not only did the group of dogs treated at 7-day intervals display a consistently higher efficacy throughout the course of the study, but the effect on mite numbers and the resolution of the clinical signs were also more rapid. The efficacy values recorded 27 days after the initiation of treatment was 34.6% for the group treated at monthly intervals and 96.0% for the group treated at 7-day intervals, indicating a statistically significant superior efficacy. The clinical appearance of dogs treated at 7-day intervals was also much improved compared to dogs treated at 28-day intervals. Two months after the initiation of the treatment, 50% of the dogs in the 7-day treatment regimen displayed a hair regrowth of > 90% compared to 25% of the 28-day treatment regimen group.

The objective of this study was not to illustrate the efficacy of Advocate® spot-on to cure dogs suffering from generalised demodicosis, but to illustrate a more rapid clinical and parasitological improvement in dogs treated at weekly compared to dogs treated at monthly intervals. Both Paradis (1999) and Burrows (2000) state that cure is defined as an animal being disease-free for at least 1 year after treatment.

The high frequency and long-term application of certain compounds used to treat dogs suffering from generalised demodicosis have resulted in side effects in some dogs (Paradis 1999; Mueller 2004). The results obtained in the safety assessment trial performed as part of this study show that changes in the values of the blood parameters are not indicative of organ damage and the clinical signs that were observed were not related to the application of the test compound. Advocate® spot-on was safe to use at five times the recommended dose under the conditions of the study. A dermal safety study with Advocate®, applied up to five times the recommended dose, demonstrated that the compound is also safe to use in the ivermectin-sensitive Collie (Paul et al. 2005).

Conclusion

Advocate® applied at weekly intervals is safe to use and results in a more rapid onset in the control of mites and the resolution of clinical signs associated with generalised demodicosis than conventional monthly treatments.

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