The efficacy of an imidacloprid/moxidectin combination against naturally acquired *Sarcoptes scabiei* infestations on dogs

LJ FOURIE[a], J. HEINE[b] and IG HORAK[a]

The study was undertaken to evaluate and compare the efficacy of an imidacloprid (10% w/v) / moxidectin (2.5% w/v) combination (Advocate® Bayer HealthCare, Animal Health) with that of selamectin for the treatment of *Sarcoptes scabiei* on dogs. Thirty naturally infested dogs, of which one was later withdrawn because of distemper, were allocated to two equal groups and individually housed. The dogs in each group were treated twice, four weeks apart, with either the combination product (0.1 mL/kg body weight) or with selamectin (0.05 mL/kg body weight) administered topically. Skin scrapings were made every 14 days over a period of 50 to 64 days after the first treatment to quantify mite numbers. Clinical signs and the extent of sarcoptic lesions were assessed on each dog when skin scrapings were made. Efficacy was based on the presence or absence of mites, supported by clinical signs associated with canine sarcoptic mange. From Day 22 and onwards no *Sarcoptes* mites were found in the skin scrapings of any of the treated dogs. Treatment with the imidacloprid/moxidectin formulation or with selamectin was highly effective against *Sarcoptes scabiei* and resulted in an almost complete resolution of clinical signs within 50 to 64 days after the initial treatment.

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Sarcoptic mange caused by the astigmatid mite *Sarcoptes scabiei* is highly contagious and is considered to be one of the most uncomfortable diseases that a dog can contract. The mites burrow in the lower stratum corneum of the epidermis and only rarely penetrate the lower epidermis or dermis.[1] Clinical signs and lesions of infestation in dogs consist of severe pruritus, papules, crusts, excoriations and alopecia.[2] Diagnosis is based on the presence of these signs, and confirmed by the recovery of mites or mite eggs. It is often difficult to demonstrate the presence of mites with skin scrapings[2], and even with multiple scrapings mites may not be recovered.[3]

The genus *Sarcoptes* apparently contains only one valid but variable species,[4] and mites from different hosts exhibit little or no morphological difference.[5] The mites appear to be host species-specific and generally cannot complete their life cycles on non-definitive hosts.[5] Host specificity may thus be due to physiological differences between scabies mites from different hosts, and immune responses induced in the host by different strains of mites may also contribute to this specificity. Humans can become infested with animal strains of scabies, and it has been estimated that a third of affected dogs transmit infestation to a person in the household.[6] These infestations are mostly self-limiting, but in rare cases canine mites have reproduced on humans.[7]

[a]Department of Zoology and Entomology, University of the Free State, Bloemfontein, 9301, South Africa
[b]Bayer HealthCare AG, Animal Health Division, D-51368 Leverkusen, Germany

Pets are seldom infested with a single parasite species, but the development of new active ingredients and the combination of these with existing compounds has made simultaneous control of a multitude of parasites with a single treatment possible. One such combination containing imidicloprid, a fairly recently synthesised neonicotinoid, and an existing macrocyclic lactone, moxidectin, has been registered for the control of helminth and arthropod parasites of dogs and cats (Advocate®: Bayer HealthCare, Animal Health). After topical application the imidacloprid moiety acts against adult fleas upon contact,[8] and the moxidectin component is absorbed transdermally and is systemically active against a variety of helminth and arthropod parasites.[9,10] The objective of this study was to determine the efficacy of this combination, applied twice, four weeks apart, to dogs with naturally acquired infestations of *Sarcoptes scabiei*. The macrocyclic lactone, selamectin, for which the efficacy against canine sarcoptic mange has already been demonstrated,[11] was included in the trial for comparative purposes and was also applied twice with an interval of 4-weeks.

Materials and methods

Animals

Thirty dogs (2.60 – 19.05 kg), older than 6 months, of both sexes (14 males and 16 females), with naturally acquired infestations of *Sarcoptes scabiei*, were purchased from their owners at various localities in South Africa. The dogs were mainly cross breeds, with hair lengths varying from short to long and except for signs of sarcoptic mange were otherwise healthy. They had no history of treatment with a parasiticide within the 8-week period preceding the first treatment and skin scrapings confirmed the presence of live mites and/or mite eggs before the start of the study.

The dogs were routinely vaccinated against common diseases and identified by numbered tags attached to their neckbands. They were individually housed under strict quarantine conditions, with no contact between dogs. Dry food pellets and fresh water were provided *ad libitum*. The housing and husbandry of the dogs were in compliance with national standards.[12]

Experimental design

The study was a randomised, controlled efficacy study, and because some of the assessment criteria were partly subjective, the study was masked and personnel were unaware of the identity of the treatment groups. All dogs were examined by a veterinarian before the start of the study and were randomly allocated to two treatment groups of 15 dogs. No dogs were kept as untreated controls because they would have had to endure a prolonged period of discomfort. Furthermore, in our experience spontaneous cure is not a regular feature of infestation with

Sarcoptes scabiei. A veterinarian also examined the dogs 27 and 49 days after treatment.

The animals were acclimatised for 7 days before the first treatment and a second treatment was administered 28 days later. All dogs were observed for four hours after treatment for possible adverse reactions and also on a daily basis for general health. Clinical evaluations, the quantification of pruritus and counts of mites were conducted three days before and at 14-day intervals after treatment.

Parasiticides

A combination of imidacloprid (10% w/v) and moxidectin (2.5% w/v) (Advocate®: Bayer HealthCare AG, Animal Health Division, Germany) was administered at 0.1 mL/kg body weight to dogs in Group 1. Selamectin (12%) (Stronghold 240 mg®: Pfizer Animal Health, Karlsruhe, Germany) was applied at 0.05 mL/kg body weight to dogs in Group 2. Both products were applied twice with an interval of 4 weeks between applications. The individual doses were based on body weights obtained the day before treatment, and were applied as a single spot with a standard disposable tuberculin syringe (0.01/1.0 mL) to undamaged skin between the shoulders. The dogs were restrained for about 1 minute after treatment to allow the compounds to spread. No healthy skin could be found on the backs or necks of four dogs, and these animals were treated on the least damaged skin surface on their backs.

Assessments

Counts of mites - Efficacy was based on the presence or absence of mites, supported by clinical signs associated with canine sarcoptic mange on the days listed above. Skin scrapings (~4 cm^2) were made on each dog from five sites showing the greatest likelihood of infestation 3 days before and 8, 22, 36 and 50 days after treatment. After one or two drops of mineral oil had been placed on the skin, scrapings were made with a scalpel blade and the material was transferred to mineral oil on microscope slides. These slides were examined under a stereoscopic microscope for live mites and mite eggs.

Clinical signs — Because of difficulties in obtaining mites for accurate counts, false negatives could have been recorded, which would have resulted in an overestimation of the success of the treatments. To counter this possibility, clinical signs were also used to support the success of treatment. Signs and the extent of sarcoptic lesions on each dog were assessed when skin scrapings were made. Areas covered by papules, scaling or crusting, hyperkeratosis and alopecia were estimated and sketched on a silhouette of each dog and the dog itself was comprehensively photographed. The skin surface area on which hair regrowth occurred was categorised as 1 if it had increased by > 80%, 2 if it was 30 to 80% greater, and 3 if its size had increased by 30% or less than the area of the alopecia observed 3 days before treatment. Pruritus was quantified by counting the number of times a dog scratched or nibbled at its body within a period of 10 minutes.

Data analysis

The numbers of mites or their eggs counted in the five skin scrapings were combined for each dog and served as the primary variable for treatment success. The success for each group was calculated from the proportion of dogs with no live mites or eggs and expressed as a percentage.

The daily average frequency of pruritus was calculated for each dog by:

$$\text{Average frequency} = \frac{\text{Area under the frequency versus time of observation curve (AUC)}}{\text{Observation period}}$$

The mean values of the average frequency were calculated for each group and compared descriptively. An ANOVA with a treatment effect was used to compare the area under the curve (AUC) values of the two groups.

Results

One dog with suspected distemper was withdrawn from the group treated with imidacloprid/moxidectin (Group 1) 16 days after the initial treatment. The presence of live mites and/or eggs was confirmed on all 30 dogs during the 5-week period before the initial treatment. Three days before the first treatment, *Sarcoptes scabiei* and/or its eggs were found in skin scrapings of 10 dogs in Group 1 and 12 dogs in the group treated with selamectin (Group 2). Eight days after this treatment they were found in the skin scrapings of two dogs in Group 1 and three in Group 2, and at 22 days and onwards no *Sarcoptes scabiei* mites or eggs were found in the skin scrapings of any of the dogs (Table 1). *Demodex canis* was present in the skin scrapings of one dog in Group 2 on all days after treatment and also in skin biopsies of two other dogs in the same group 64 days after treatment.

The percentage of dogs in each group with papules, scaling/crusting, hyperkeratosis and alopecia on the skin on the different days after treatment are summarised in Tables 2 and 3. By Day 36 papules and scaling/crusting on the skin of the majority of dogs had markedly decreased, but hyperkeratosis was still present. By Day 50 hair regrowth had improved by more than 80% in all 14 dogs (100%) in Group 1 and in 11 (80%) of the 15 dogs in Group 2.

Table 1. Total counts of *Sarcoptes scabiei* on dogs treated with either imidacloprid/moxidectin (Group 1) or selamectin (Group 2)

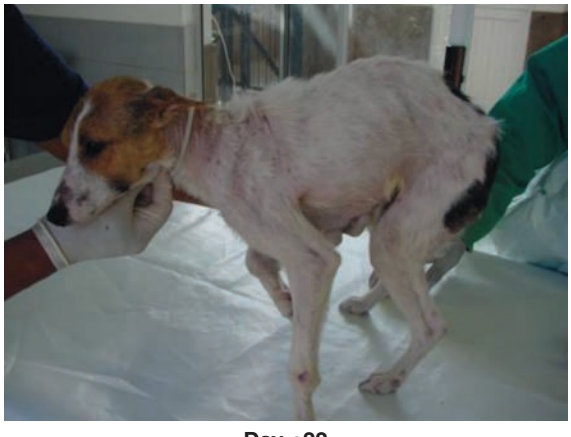
Days after treatment	Group 1			Group 2		
	Mites	Eggs	Dogs infested	Mites	Eggs	Dogs infested
-3	1 235	677	10/15	234	257	12/15
8	7	1	2/15	179	139	3/15
22	0	0	0/14	0	0	0/15
36	0	0	0/14	0	0	0/15
50	0	0	0/14	0	0	0/15
64[a]	0	0	0/1	0	0	0/4

[a]One dog in Group 1 and four dogs in Group 2 still affected clinically and retained until Day 64 after initial treatment.

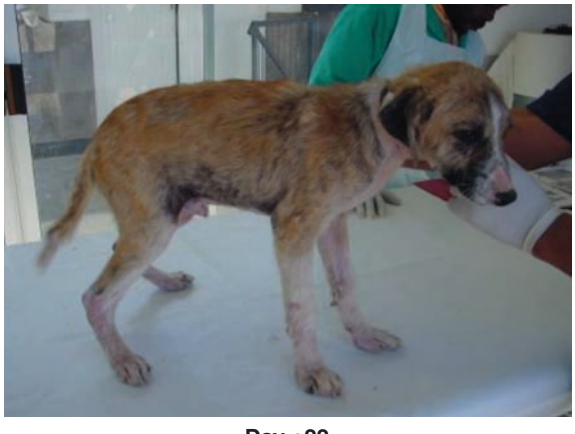
The mean pruritus score in Group 1 increased from 6.8 to 8.8 by Day 22 and then decreased to 2.1 at Day 49. For dogs in Group 2 it decreased consistently from 6.9 to 2.7 by Day 49. The AUC (0 - 49 d) for Groups 1 and 2 was 279.5 and 204.9 respectively, and the AUC (0 to 49 d)/49 was 5.7 and 4.2 respectively. The indices of the two groups were not significantly different (P = 0.29), and the lower and upper 90% confidence intervals were -0.87 and 3.91 respectively, indicating that there was no significant differ-

Day -3

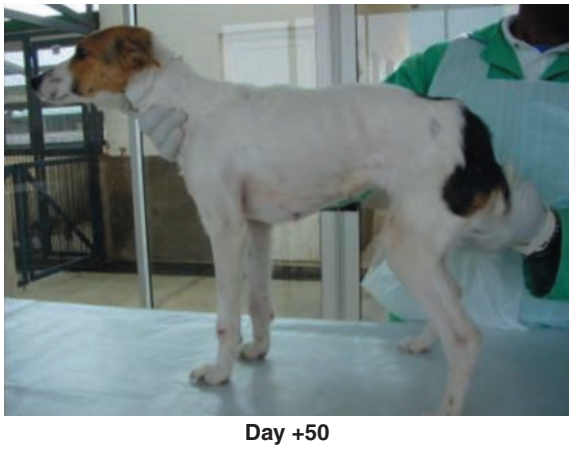
Day -3



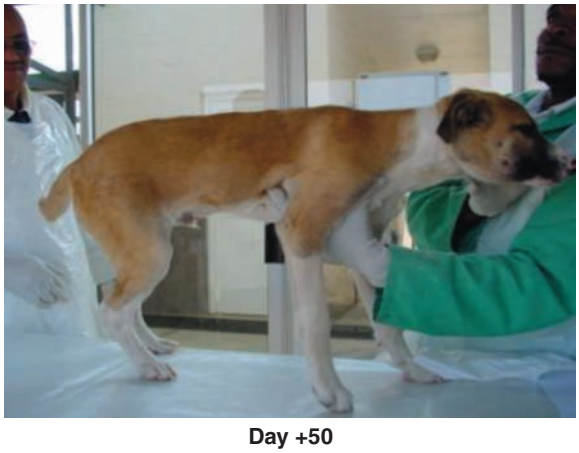
Day +22



Day +22



Day +50



Day +50

Plate 1. Resolution of sarcoptic mange over a period of 50 days on two dogs treated with an imidacloprid (10%) / moxidectin (2.5%) combination at a dose of 0.1 mL/kg body weight on Days 0 and 28, respectively.

Table 2. Resolution of skin lesions caused by *Sarcoptes scabiei* on dogs treated with either imidacloprid/moxidectin (Group 1) or selamectin (Group 2)

Skin lesions	Percentage of dogs affected									
	Group 1					Group 2				
	Days after initial treatment					Days after initial treatment				
	8	22	36	50	64[a]	8	22	36	50	64[a]
Papules	36	36	0	0	0	47	33	7	0	0
Scaling/crusting	71	21	7	0	0	67	53	7	7	13
Hyperkeratosis	57	50	57	50	50	80	60	60	47	47

[a]One dog in Group 1 and four dogs in Group 2 were still affected clinically and retained for extended periods of observation

Table 3. Hair regrowth on dogs at different times after initial treatment for *Sarcoptes scabiei* with either imidacloprid/moxidectin (Group 1) or selamectin (Group 2)

Hair regrowth score[a]	Percentage of dogs affected									
	Group 1					Group 2				
	Days after initial treatment					Days after initial treatment				
	8	22	36	50	64[b]	8	22	36	50	64[b]
1	0	7	43	100	100	0	7	27	73	80
2	7	29	36	0	0	13	26	40	20	13
3	93	64	21	0	0	87	67	33	7	7

[a]Hair regrowth scores relative to initial assessment: 1 > 80%, 2 = 30 to 80%; 3 < 30%
[b]One dog in Group 1 and four dogs in Group 2 were retained for extended periods of observation.

ence between the two compounds in their effect of decreasing pruritus.

Photographs in Plate 1 show the marked improvement in both lesions and physical condition of most of the dogs after treatment. Clinical signs associated with mange did not completely resolve in one dog in Group 1 and five dogs in Group 2. Five of these dogs were retained for extended observations, but at Days 57 and 64 after initial treatment the growth of hair had improved only slightly and patches of dermatitis were still visible. Skin biopsies for histopathological evaluation taken from four of these dogs indicated an hypersensitive dermatitis in two dogs (one each in Group 1 and 2) and *Demodex canis* infestation, hyperkeratosis and acanthosis in the other two dogs.

Although no mites or eggs were recovered from skin scrapings from any of the dogs from Day 22 onwards, noticeable improvement in clinical signs was only apparent from Day 36 onwards (Tables 2 and 3). Based on the absence of *Sarcoptes* mites in skin scrapings and almost complete resolution of clinical signs, success for both compounds was assessed as 100%.

Because of the severity of their mange and the novelty of their surroundings many of the dogs initially appeared lethargic. As they became accustomed to the kennels and the treatment started to take effect the behaviour of most animals improved. This was visible in all but the most severely affected dogs by 10 days after treatment, and by Day 30 the appetite and behaviour of all dogs were considered normal. No adverse reaction to the application of either treatment was noted.

Discussion

Sarcoptic mange occurs in dogs of any age, breed, hair length, or sex,[3] and the gross dermatological signs vary with progression of the infestation.[13] Furthermore, the occurrence of signs may vary between specific dogs or dog breeds,[13,14] and some dogs never display the classic lesions associated with scabies.[14] In this study the numbers of mites recovered from animals were not related to the extent of clinical signs, and dogs with extensive alopecia and high pruritus scores did not have the highest counts of mites. Mites can be difficult to demonstrate in dogs that are intensely pruritic and have had the infestation for a long time.[14] This is consistent with the findings of this study.

Assessment of efficacy in the present study was based on both estimates of mite numbers and evaluation of clinical signs associated with the mange. A similar approach has been followed in efficacy studies by other researchers.[11] The life cycle (egg to adult) of *Sarcoptes scabiei* is completed within 10 to 13 days.[5] In experimentally infested dogs, the clinical signs of disease start soon after infestation, but the areas of skin showing lesions increase steadily over an 8-week period.[13] The present study extended over 50 to 64 days thus allowing ample time for mite numbers to increase, should treatment not have been effective. In addition, five to six skin scrapings were made at intervals of 14 days to ascertain the presence or absence of mites.

Although the resolution of clinical signs of sarcoptic mange in dogs has been used to support claims on the treatment success of compounds,[11,15] the persistence of some clinical signs does not necessarily indicate a treatment failure and must therefore be viewed with caution. In this study the pruritus scores of most dogs (59%) were highly variable, and in only about 41% of dogs did pruritus decrease after treatment. For example, some dogs with high mite counts before treatment had a zero or low pruritus score initially. The persistence of pruritus, albeit be it mild, in some dogs considered to be free of mites, has been reported by

other investigators.[2,11] In an efficacy study on a 10% imidacloprid solution against sucking and biting lice (*Linognathus setosus* and *Trichodectes canis*) on dogs, pruritus caused by the lice was seen even in the absence of lice for up to 4 weeks after treatment.[16] This supports the contention of some authors that persistent pruritus may be due to hypersensitivity to the antigens released by dead and decomposing ectoparasites.[3] Consequently, the persistence of mild pruritus after treatment does not necessarily indicate that the treatment was unsuccessful and should be viewed with circumspection. Conversely, severe constant pruritus may be an important clinical sign implying potential infestation with *Sarcoptes* or other mites.

By 50 days after initial treatment with the imidicloprid/moxidectin solution the clinical signs attributable to sarcoptic mange had almost disappeared. Three dogs treated with selamectin had mild alopecia whereas small, localised areas of scaling/crusting were still present on two other dogs. Other skin diseases, and reactions to ectoparasites such as fleas and *Demodex* spp. mites, as well as allergic reactions, resemble the signs of scabies and may even influence its clinical appearance.[13] The persistent alopecia on three dogs treated with selamectin can most probably be attributed to concurrent infestations with *Demodex* spp. mites as confirmed by skin scrapings and skin biopsies. Alopecia, scaling/crusting and pyoderma are common signs of generalised demodicosis.[2,14]

Treatment of canine scabies is achieved by the administration of an effective acaricide. Both affected and in-contact animals should be treated, and in addition the application of a suitable acaricide to the animal's bedding and housing is advocated.[17] Previously registered topical parasiticides were typically used once a week for 4 to 6 weeks, and the clipping of hair from affected areas and the use of an anti-seborrhoeic shampoo before application of the parasiticide is recommended.[14,17] The use of these parasiticides is labour intensive and thus may be associated with low owner compliance. Furthermore, many of these compounds are no longer available. The products currently in use are far safer for animals and the environment than those used five years ago,[14] and efficacy has also improved through the use of modern delivery systems.

The extra-label use of macrocyclic lactones administered either orally or via sub-cutaneous injection is effective in the treatment of canine scabies.[18,19] Moxidectin, administered at 0.2 to 0.25 mg / kg body weight either orally or subcutaneously at weekly intervals for three to six weeks, has proved highly effective in curing sarcoptic mange on dogs.[20] Selamectin, administered twice topically with a 30-day interval is effective in the treatment of canine scabies,[11] and the same result was obtained in the present study. This study has also shown that a combination of imidacloprid 10% and moxidectin 2.5% applied twice topically at a monthly interval, is highly effective against *Sarcoptes scabiei* in dogs and resulted in an almost complete resolution of the skin lesions typical of this disease.

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