

Therapeutic Evaluation of Topical Tacrolimus for the Management of Canine Atopic Dermatitis (CAD) - A Clinical Study

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Abstract

A blind folded randomized control study was designed to evaluate the efficacy of topical application of Tacrolimus spray in treating Canine Atopic Dermatitis (CAD). The group A dogs were treated with topical tacrolimus spray showed significant changes on the fourth week as compared to that of the placebo (Group B) and complete recovery along with clinical resolution of lesions was recorded.

Keywords: Canine atopic dermatitis; tacrolimus; topical

Introduction

Canine atopic dermatitis (CAD) is a common, recurring, inflammatory and pruritic allergic skin disease in dogs exhibiting characteristic clinical signs associated with IgE antibodies that is most commonly directed against environmental allergens (Halliwell, 2006). It is the second most common allergy in dogs (10% of canine population) (Scott *et al.*, 2001) and frustrating problem in Veterinary dermatology. The hallmark signs of CAD are constant pruritis (Reedy *et al.*, 1997). Though CAD is commonly encountered, the therapeutic options to treat the animal affected with CAD are scares. It is initially treated with glucocorticoids, which is now replaced by Cyclosporine due to adverse side effects and has proven to be effective in managing atopic dermatitis (Olivry *et al.*, 2002a and Olivry *et al.*, 2002b). Adverse reactions like vomiting and diarrhea has been reported in a few cases with Cyclosporine (Steffan and Parks, 2005) which eventually forced the owner to discontinue the use of Cyclosporine. Topical tacrolimus is an immunomodulator. Tacrolimus (FK-506) is a calcineurin inhibitor currently approved to treat moderate to severe atopic dermatitis (AD) (Marsella *et al.*, 2004). With this background the present study was taken to evaluate the efficacy of topical tacrolimus spray (Takfa pet^a) in treating the canine atopic dermatitis with localized lesions.

Materials and Methods

The study was conducted on client owned dogs with CAD during period of one year (2014-2015) with the owner's consent. Dogs presented with history of severe recurrent pruritus (seasonally or throughout the year) were screened for Canine Atopic Dermatitis (CAD).

Inclusion criteria : Suspected dogs were subjected to following diagnostic criteria of Canine Atopic Dermatitis based on Favrot *et al.* (2010) (after thorough ruling out other causes like parasites, malassezia, bacteria, flea allergy, chemical allergy and food allergy) 1. Onset of signs under three years of age, 2. Dog living mostly indoors 3. Glucocorticoid responsive pruritus, 4. Pruritus sine materia at onset (*i.e.* aseasonal pruritus), 5. Affected front feet, 6. Affected ear pinnae, 7. Non affected ear margins, 8. Non affected dorso-lumbar area. Combinations of any five satisfied criteria of clinical features were taken into study. Intra-dermal testing or identification of allergen-specific IgE serology is not required for diagnosis of CAD, as recommended by ACVD Task Force on Canine AD (DeBoer and Hiller, 2001). Dogs with localized skin lesion such as pododermatitis, facial lesions, ear pinna erythema or ventral abdominal lesions were taken for the study.

The suspected dogs were subjected to routine clinical examination and detailed dermatological investigations (skin scraping, trichogram, tape impression). All the resembling or co-existing diseases were ruled out. Initially all dogs were treated for flea with flea treatment, irrespective of the prevailing condition, followed by dietary trial in all dogs under study for a period of eight weeks. Dog

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Fig. 1: Peri labial, Front paw, Inguinal lesions in CAD

Fig. 2a: Before treatment Fig. 2b: After treatment
Fig. 2: Foot lesions in CAD

Fig. 3a: Before treatment



Fig. 3b: After treatment

Fig. 3: Ear erythema in CAD

that showed no response to dietary trial alone are taken into study after clearing the secondary bacterial and yeast infestation with appropriate antibiotics and antifungals. Dogs were instructed to be bathed with non medicated shampoo. Oral, topical or injectable glucocorticoids were discontinued for at least six weeks prior to the study. Antihistaminics and topical treatments for two weeks and cyclosporine for one month were avoided before the commencement of trial.

Exclusion criteria: Unexpected use of antihistaminics, glucocorticoids by the owners to dogs under study; Sudden flare up with active yeast and bacterial infection during the study; unagreeable adverse effects of drug under study; Due to unavoidable reasons incomplete treatment given by the owner (Marsella and Nicklin, 2002).

Design of study: Out of 90 suspected animals, 52 dogs were diagnosed to have CAD. Among 52 dogs, 30 dogs with localized lesions of atopic dermatitis were selected for the study. Using lot method these 30 dogs were randomly allocated into two groups, comprised of 20 dogs in treatment group and 10 dogs in placebo group. The evaluating clinician was unaware of the treatment assignment throughout the

study with the randomization sequence, being kept by another staff of the clinic. Neither the clinician nor the investigator was aware as which animal was the treatment or the control until the completion of study (Marsella and Nicklin, 2002). In the treatment group, all the 20 dogs were subjected to topical therapy with Takfa pet spray^a (Tacrolimus 0.02%) twice daily for four weeks on the pruritic lesion areas. Lesions scores was assessed on 0th 2nd and 4th weeks with CADESI 4 (ICADA2013) for all the dogs under study (Olivry *et al.*, 2014). Therapeutic efficacy of Tacrolimus spray 0.02% was evaluated by monitoring the days required for clinical recovery. As a measure of successful treatment, the lesional scores between Tacrolimus and placebo was done to compared the percentage of change from the base line. Response for therapy was assessed to see how many animals showed 50% or greater reduction in scores at the end of the study

Statistical Analysis

The data obtained between treatment group was analysed using unpaired t-test and one way analysis of variance was applied to analysis the results obtained between weeks among the treatment group.

Table 1: Evaluating the efficacy of Tacrolimus 0.02% topical spray in CAD (unpaired t test)

Week	Tacrolimus	Placebo	T value
Week 0	29.85±1.413	28.70 ±1.453	0.51 ^{NS}
Week 2	18.65±0.966	28.50±1.522	5.671 ^{**}
Week 4	9.90±0.486	28.50±1.522	14.714 ^{**}

** : Highly significant difference ($P \leq 0.01$ percent)

NS: Non-significant

Result and Discussion

Among 90 dogs that were presented to our clinic with history of constant pruritus and lesions with erythema, 52 dogs were identified to be suffering from CAD based on Favrot *et al.* (2010) criteria after ruling out other causes. These dogs were evaluated for identifying localized or generalized CAD. Based on selection criteria, 30 localized atopic dermatitis cases were selected. Cases under study showed erythema, lichenification, excoriation and alopecia, these lesions were identified as lesions in different parts of body such as pedal dermatitis 100%, facial lesion 90%, ear pinna 100% and ventral abdomen 60%. This is in agreement with the studies by Muse *et al.* (1996), Reedy *et al.* (1997) and Olivry and Sousa (2001).

Olivry *et al.* (2010) reported distribution of CAD skin lesions were variable and depend upon chronicity of disease and allergens involved. Jaeger *et al.* (2010) reported that the most commonly affected skin sites of dogs with AD were paws (62 percent). In the present study, paws were affected in all dogs. Zur *et al.* (2012) observed that most of the dogs (82.9 percent) had lesions on ventral part of body. Sixty eight percent (67.7 percent) had lesions on their feet and in 61 percent of dogs, the ventrum was also affected. Lesions and/or facial pruritus were observed in 41 percent of the dogs (Fig 1a, 2a, 3a).

Among breeds, the prevalence of CAD in present study was found to be more prominent in Labrador Retrievers (70%), followed by Pug (21%), Great Dane (5%) and non descript (4%). Similar findings were reported by various authors, like Williemse (1996) and Bizikova *et al.* (2015) described the genetic predisposition of CAD in breeds such Labrador Retriever and Pug.

In this study the onset of clinical signs ranged from 5 months to 3 years of age. Similar findings were

Table 2: Statistical analysis of weekly evaluation of Tacrolimus topical spray in Canine Atopic Dermatitis – one way- ANOVA

Drug	Week 0	Week 2	Week 4	F value
Tacrolimus	29.85 ^c ±1.412	18.65 ^b ±0.965	9.90 ^a ±0.486	94.772 ^{**}
Placebo	28.70±1.453	28.50±1.522	28.50±1.522	0.006 ^{NS}

Means bearing different superscripts differ from each other

** : Highly significant difference ($P \leq 0.01$ percent)

NS: Non- significant

observed Griffin and DeBoer (2001) and Bizikova *et al.* (2015).

Following therapy with Takfa pet^a, improvement in erythema, pruritus, absence of papule, pustule, excoriations, urticaria, otitis externa and crusts started from 14th day with major clinical improvement by 28 days after treatment. After two weeks of therapy, all dogs showed more than 50% of improvement from baseline.

The affected dogs showed decrease in itching at days after the start of treatment and 90% reduction in pruritus was noticed in dogs at the end of four weeks. It seems that local application of Tacrolimus spray was useful in reducing severity of localized skin lesions.

There was a significant difference in the investigator's score for erythema and pruritus on 4th week between treatment group and placebo. There was no significant difference between the treatment groups on week 0, however highly significant difference was observed on 2nd week and 4th week between group A (Tacrolimus) and group B (Placebo) (Table 1) (Fig 1b, 2b, 3b). Among the treatment group A (Tacrolimus) significant difference was noticed between weeks, whereas the difference among weeks in group B (placebo) was non significant (Table 2).

Castro and Pediatr (2006) stated that Tacrolimus binds with calmodlin by penetrating the membrane of inflamed cells associated with atopic dermatitis and inhibits synthesis of calcineurin in lymphocytes, dendritic cells, basophils and eosinophils, Remitz *et al.* (2001) stated that Tacrolimus reduced the *Staphylococcus* population in atopic patients treated tacrolimus, while Simpson and Noble (2005) reported fungicidal activity of tacrolimus against *Malassezia furfur* in AD especially in head and neck region.

The only adverse effect was a burning sensation expressed by a couple of owners for a few days on initiation of treatment, but resolved by itself after 4 days of continuous use, which is supported by Marsella and Nicklin (2002) who stated that it could be due to the molecular weight of Tacrolimus is such that it penetrates through inflamed skin and hardly penetrated the epidermis of normal skin. Therefore it was hypothesized that, once inflammation reduces the compound will be penetrating less thus limiting the risk of adverse effects.

Tacrolimus is one of the group relatively new drug called calcineuron inhibitors which has both anti-inflammatory and immuno-suppressive or immuno-modulator property. The mechanism of action is through the inhibition of calcium dependent pathways that effect enzymatic action of calcineuron. This in turn blocks proliferation of T lymphocytes and cytotoxic cells. Nakagawa *et al.* (1994) reported the successful use of topical Tacrolimus in humans with atopic dermatitis. Preliminary study by Marsella and Nicklin (2002) documented as topical use of 0.3% Tacrolimus is safe and is minimally absorbed despite its potency. Marsella *et al.* (2004) indicated that tacrolimus significantly decreased pruritus and erythema using Tacrolimus (0.02%) in a compounded lotion formulation for four weeks and further reported that topical Tacrolimus has better absorption by easily penetrating through skin and has rapid onset of action and exerts sustaining therapeutic effects, with an efficacy similar to that of moderate to potent topical corticosteroid but without causing skin atrophy. In the present study, 33% clinical improvement was noticed as early as 2nd week and 67% improvement by 4th week whereas clinical improvement reported by Bensignor and Olivry. (2005) on 2nd and 4th week were 30% and 50% respectively. This might be due to the lipid based preparation of topical Tacrolimus spray which augments the rapid absorption through the skin when compared to ointment base. In conclusion, tacrolimus spray was found to be more effective in treating canine atopic dermatitis with localized lesions.

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References

- Bensignor, E. and Olivry, T. (2005). Treatment of localized lesions of canine atopic dermatitis with tacrolimus ointment: a blinded randomized controlled trial. *Vet Dermatol.* **16**: 52-60.
- Bizikova, P., Pucheu-Haston, C., Eisenschenk, M., Marsella, R., Nuttall, T. and Santoro, D. (2015). Review: Role of genetics and the environment in the pathogenesis of canine atopic dermatitis. *Vet. Dermatol.* **26**: 95-e26.
- Castro, A.P.B.M. and Pediatr, J. (2006). Calcineurin inhibitors in the treatment of allergic dermatitis. *Rio J.* **82**: 166-72.
- DeBoer, D.J. and Hillier, A. (2001). The ACVD task force on canine atopic dermatitis (XVI): laboratory evaluation of dogs with atopic dermatitis with serum -based "allergy" tests. *Vet. Immunol. Immunopathol.* **81**: 277-87.
- Favrot, C., Steffan, J., Seewald, W. and Picco, F. (2010). A prospective study on the clinical features of chronic canine atopic dermatitis and its diagnosis. *Vet. Dermatol.* **21**: 23-30.
- Griffin, C.E and DeBoer, D.J. (2001). The ACVD task force on canine atopic dermatitis (XIV): clinical manifestations of canine atopic dermatitis. *Vet. Immunol. Immunopathol.* **81**: 255-69.
- Halliwell, R. (2006). Revised nomenclature for veterinary allergy. *Vet. Immunol. Immunopathol.* **114** : 207-08.
- Jaeger, K., Linek, M., Power, H.T., Bettenay, S.V., Zabel, S., Rosychuk, R.A.W. and Mueller, S.R. (2010). Breed and site predispositions of dogs with atopic dermatitis: a comparison of five locations in three continents. *Vet. Dermatol.* **21**: 118-22.
- Marsella, R and Nicklin, C.F. (2002). Investigation on the use of 0.3% tacrolimus lotion for canine atopic dermatitis: a pilot study. *Vet Dermatol.* **13**: 203-10.
- Marsella, R., Nicklin, C.F., Saglio, S. and Lopez, J. (2004). Investigation on the clinical efficacy and safety of 0.1% tacrolimus ointment (Protopic) in canine atopic dermatitis: a randomized, double-blinded, placebo-controlled, cross-over study. *Vet. Dermatol.* **15** : 294-03.
- Nakagawa, H., Etoh, T. and Ishibashi, Y. (1994). Tacrolimus ointment for atopic dermatitis. *Lancet* **344**: 883.
- Olivry, T and Sousa, C.A. (2001). The ACVD task force on canine atopic dermatitis (VIII): general principles of therapy. *Vet. Immunol. Immunopathol.* **81**: 317-22.
- Olivry, T., Rivierre, C. and Jackson, H.A. (2002a). Cyclosporine decreases skin lesions and pruritus in dogs with atopic dermatitis: a blinded randomized prednisolone-controlled trial. *Vet. Dermatol.* **13**: 77-87.

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- Olivry, T., Steffan, J., Fisch, R.D., Prelaud, P., Guaguere, E., Fontaine, J. and Carlotti, D.N. **(2002b)**. European Veterinary Dermatology Ciclosporin Group. Randomized controlled trial of the efficacy of cyclosporine in the treatment of atopic dermatitis in dogs. *J. Am. Vet. Med. Assoc.* **221**: 370-77.
- Olivry, T., DeBoer, D.J., Favrot, C., Jackson, H.A., Mueller, R.S., Nuttall, T. and Prélaud, P. **(2010)**. Treatment of canine atopic dermatitis: 2010 clinical practice guidelines from the International Task Force on Canine Atopic Dermatitis. *Vet. Dermatol.* **20**: 233-48.
- Olivry, T., Saridomichelakis, M., Nuttall, T., Bensignor, E., Griffin C.E. and Hill, P.B. **(2014)**. Validation of the Canine Atopic Dermatitis Extent and Severity Index (CADESI)-4, a simplified severity scale for assessing skin lesions of atopic dermatitis in dogs. *Vet. Dermatol.* **25**: 77-e25.
- Reedy L.M., Miller, J.W.H. and Willemse, T. **(1997)**. Allergic Skin Diseases of Dogs and Cats. Saunders, Philadelphia.
- Remitz, A., Kyllonen, H., Granlund, H. and Reitamo, S. **(2001)**. Tacrolimus ointment reduces staphylococcal colonization of atopic dermatitis lesions. *J. Allergy Clin. Immunol.* **107**: 196.
- Scott, D.W., Miller, W.H. and Griffin, C.E. **(2001)**. Canine atopic disease. In: *Muller & Kirk's Small Animal Dermatology*, Sixth Ed. W.B. Saunders, Philadelphia, PA, USA, p. 574-601.
- Simpson, D. and Noble, S. **(2005)**. Tacrolimus ointment: a review of its use in atopic dermatitis and its clinical potential in other inflammatory skin conditions. *Drugs.* **65**: 827-58.
- Steffan, J. and Parks, C. **(2005)**. Clinical trial evaluating the efficacy and safety of cyclosporine in dogs with atopic dermatitis. *J Am Vet Med Assoc* **226**: 1855-63.
- Wilhem, S., Kovalik, M. and Favrot, C. **(2011)**. Breed-associated phenotypes in canine atopic dermatitis. *Vet. Dermatol.* **22**: 143-49.
- Zur, G., Skorinsky, I. and Bdolah-Abram, T. **(2012)**. Canine atopic dermatitis in the Middle East: clinical signs, signalment and common allergens. *Veterinarni Medicina* **57**: 410-19.



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