

Results of allergen-specific immunotherapy in atopic dogs with *Malassezia* hypersensitivity: a retrospective study of 16 cases

Liselotte Åberg* , Katarina Varjonen† and Susanne Åhman*

*Djurakuten i Stor-Stockholm AB, Kungstensgatan 58, 113 29 Stockholm, Sweden

†Royal (Dick) School of Veterinary Studies, Small Animal Hospital, University of Edinburgh, Easter Bush Campus, Roslin, EH25 9RG, UK

Correspondence: Liselotte Åberg, Djurakuten i Stor-Stockholm AB, Kungstensgatan 58, 113 29 Stockholm, Sweden. E-mail: liselotte.berg@gmail.com

Background – Hypersensitivity reactions to *Malassezia* spp have been shown to occur in dogs with atopic dermatitis (AD) and to cause exacerbation of clinical signs. Improvement of clinical signs following use of antifungal medication is seen with both *Malassezia* overgrowth or *Malassezia* hypersensitivity (MHS). Subcutaneous immunotherapy (SCIT) is considered a safe and effective treatment for management of canine AD. Adverse effects are considered rare.

Objectives – To report on the use of SCIT with *Malassezia* extracts in mono-sensitized dogs.

Animals – Sixteen client owned dogs diagnosed with MHS and treated with SCIT.

Methods – A retrospective review of medical records of atopic dogs diagnosed with MHS, mono-sensitized for *Malassezia* allergens on intradermal test and treated with SCIT for more than 10 months. Efficacy was measured by decreasing use of anti-inflammatory and antifungal medication by $\geq 50\%$ and by decreasing pruritus by $\geq 50\%$ as assessed by owners, using a pruritus score.

Results – Good response to SCIT was seen in nine of 16 cases (56%) with both a reduction in use of anti-inflammatory and antifungal medication as well as a reduction in pruritus scores by $\geq 50\%$. No adverse effects were reported.

Conclusion – Allergen-specific immunotherapy was a safe treatment for dogs with *Malassezia* hypersensitivity. The efficacy of *Malassezia* immunotherapy corresponds well to the results of previous studies of immunotherapy with other environmental allergens.

Introduction

Malassezia pachydermatis is a lipophilic nonlipid-dependent yeast, that colonizes skin and mucosa of healthy dogs. It forms part of the normal microflora, but may under certain conditions act as a pathogen.¹ *Malassezia* spp. play multiple roles in the pathogenesis of human atopic dermatitis (AD). *Malassezia* dermatitis and immunoglobulin E (IgE)-mediated hypersensitivity to *Malassezia* spp may cause exacerbation of clinical signs.^{2–4} Hypersensitivity to *Malassezia pachydermatis* also occurs in atopic dogs; hereafter designated as MHS.^{5–9} Improvement of clinical signs following use of antifungal medication is seen in both human and canine atopic individuals.^{10–13}

Allergen-specific immunotherapy (ASIT) is considered a safe and effective treatment of canine atopic dermatitis (CAD). Efficacy of 50–100% is reported in open uncontrolled studies.^{14,15} Adverse reactions are rare, but include pruritus, anxiety, hyperactivity and anaphylaxis.¹⁵ Good response to ASIT in *Malassezia*-sensitized dogs has been reported anecdotally, but to best of the authors' knowledge, no clinical studies reporting on the efficacy and safety of such treatment have been published to date.¹⁶ The aim of this retrospective study was to report the clinical response and adverse effects of subcutaneous immunotherapy (SCIT) with *Malassezia* extract in atopic dogs, mono-sensitized to *Malassezia*.

Materials and methods

Records from two practices were searched, between January 2011 and May 2016, for dogs treated with SCIT containing *Malassezia* extract only. All dogs had a clinical diagnosis of AD based on published criteria.¹⁷ Ectoparasites had been ruled out. All dogs had undergone an eight week strict dietary trial, followed by a dietary re-challenge. Dogs diagnosed with food-induced atopic dermatitis (FIAD) were included in the study if strict adherence to diet had been shown to be insufficient to control clinical signs, and FIAD was considered well controlled. Additionally, all included dogs were deemed to be mono-sensitized to *Malassezia* based on positive reactions on intradermal testing (Artuvetrin®Test, 100 µg/mL, ArtuVet Animal

Abbreviations: AD, atopic dermatitis; MD, *Malassezia* dermatitis; MO, *Malassezia* otitis; HPF, high-power field; FIAD, food-induced atopic dermatitis.

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Health BV; Lelystad, Netherlands) and treated with SCIT with *Malassezia* extract (Artuvetrin®, 100 µg/mL, ArtuVet Animal Health BV) 1 mL per month or dose-adjusted based on clinical response, for a minimum of 10 months. Exclusion criteria were uncontrolled adverse food reactions and dogs with multiple positive intradermal test reactions.

Records were assessed for evidence of *Malassezia* dermatitis (MD) and otitis (MO). Diagnosis was based on clinical examination and presence of *Malassezia* spp. on cytological evaluation, more than five organisms per high-power field (HPF) for skin and >10 per HPF for ears.

Clinical response to antifungal and anti-inflammatory therapy was recorded before and after at least 10 months of SCIT. Dogs were considered to show a good response to SCIT if the use of antifungal and anti-inflammatory drug dosages and frequency were reduced by ≥50%. Additionally, if dogs, according to records, were nonpruritic or had the same level of pruritus after 10 months of SCIT, they were considered responsive and nonresponsive, respectively. If this was not stated in the records, the owner was contacted and asked to estimate the pruritus pre- and post-SCIT, from a pruritus Visual Analog Scale (PVAS). If the decrease of pruritus was ≥50%, the dog was considered to have responded to SCIT.

Results

Signalment and clinical data

The search identified 16 cases fulfilling the inclusion criteria. Sex, breed and ages are reported in Table 1. Four dogs were diagnosed with FIAD in addition to MHS. The mean age when starting SCIT was two years (range 1–6 years).

Status and therapy prior to SCIT

Malassezia otitis had previously been diagnosed in 12 of 16 dogs; 13 of 16 dogs had been diagnosed with MD. For two dogs (cases 4 and 15) there was no recorded cytological evidence consistent with MO or MD (Table 1).

Monotherapy using an antifungal shampoo showed good response in three of four dogs (cases 3, 5 and 15). Response to combined topical antifungal shampoo and anti-inflammatory medication was recorded in 14 of 16 cases. Case 12 responded to topical anti-inflammatory

treatment solely. Case 4 did not respond to topical treatment (Table 1). No dogs received systemic antifungal therapies prior to SCIT.

Response to SCIT

Good response to SCIT was seen in nine of 16 cases (56%), with a ≥50% reduction in antifungal treatment and anti-inflammatory medication (Appendix S1). All owners reported a decrease in pruritus of ≥50%.

Poor response was seen in seven of 16 cases. Increased use of anti-inflammatory treatment was noted in three of seven cases (4, 6 and 12) and systemic antifungal maintenance treatment was added in Case 6. Of the cases with limited response to treatment, two of seven owners had continued SCIT (cases 2 and 12). Case 4 showed, following discontinuation of SCIT, a marked increase in pruritus within three months. No change in pruritus was noticed in the others.

In three dogs (cases 1, 3 and 6) the dose of SCIT had been adjusted to 1 mL every three weeks, 1 mL every three weeks and 0.8 mL every three weeks, respectively. No adverse effects were recorded. Dogs responsive to SCIT were maintained on the treatment.

Pruritus scores pre- and post-SCIT are given in Appendix S1.

Discussion

In this study, nine of 16 dogs showed a good response to SCIT with *Malassezia* extract based upon a reduction in pruritus, and a reduction of concurrent topical and systemic antifungal treatment by ≥50%. Although the number of dogs fulfilling the inclusion criteria in this study is low, the results indicate that the efficacy of SCIT with *Malassezia* extracts corresponds well to the results of previous studies of immunotherapy using environmental allergens.^{14,15}

Malassezia spp. are considered to be part of the normal flora of the skin and mucous membranes. Reduction of

Table 1. Description of cases and their responses to antifungal therapies and *Malassezia* immunotherapy.

Case	Breed	Age (years)	Sex	FIAD	MO	MD	Response to topical antifungal therapy	Response to topical antifungal + anti-inflammatory therapy	Response to SCIT
1	German shepherd dog	2	F	No	Yes	Yes	N/A	Yes	Yes
2	Old Danish pointer	2	M	No	Yes	Yes	N/A	Yes	No
3	American cocker spaniel	1	F	No	NR	NR	Yes	Yes	Yes
4	Bedlington terrier	2	M	No	No	Yes	No	No	No
5	Welsh terrier	2	F	No	Yes	Yes	Yes	Yes	Yes
6	Staffordshire bull terrier	3	F	No	Yes	Yes	N/A	Yes	No
7	Flat coated retriever	3	F	No	Yes	Yes	N/A	Yes	Yes
8	Mixed breed	2	MC	No	No	Yes	N/A	Yes	Yes
9	German shepherd dog	3	F	No	Yes	Yes	N/A	Yes	No
10	Spanish water dog	2	M	Yes	Yes	No	N/A	No	No
11	German shepherd dog	3	MC	Yes	Yes	Yes	N/A	Yes	Yes
12	Schapendoes	6	F	Yes	Yes	Yes	N/A	N/A	No
13	German shepherd dog	2	M	No	Yes	Yes	N/A	Yes	Yes
14	French bulldog	2	F	No	Yes	Yes	N/A	Yes	Yes
15	French bulldog	3	M	No	NR	NR	Yes	Yes	No
16	Cocker spaniel	2	MC	Yes	Yes	Yes	N/A	Yes	Yes

MC male castrated, FIAD food-induced atopic dermatitis, MO *Malassezia* otitis, MD *Malassezia* dermatitis, NR not recorded, N/A not applicable, SCIT subcutaneous immunotherapy.

yeast can be achieved temporarily using antifungal medication and this is a recognized treatment in animals with MHS.^{1,10–13} In our study, three of four dogs responded to topical antifungal shampoo as monotherapy. Topical treatment is time-consuming and often difficult to maintain on a long-term basis for owners. Adverse effects from long-term management with systemic antifungal drugs, as well as selection of fungal strains resistant to antimicrobial drugs, are possible concerns over time.^{18,19} SCIT treatment allowed for a marked reduction of antifungal medication as well as anti-inflammatory treatment in the majority of cases in this study, reducing the risk of adverse effects from drugs as well as the need for topical treatment in management of MHS.

Seven cases were considered to be nonresponsive to SCIT. In Case 4, the owner discontinued immunotherapy after two years due to lack of improvement and as a reduction in anti-inflammatory medication had not been possible. However, within three months after discontinuing SCIT, the dog's condition deteriorated despite intensified therapy. It is possible that SCIT had some effect in this dog despite the perceived poor response. Most of the dogs which were unresponsive to SCIT responded to a combination of antifungal and anti-inflammatory therapy. It seems likely that other causes contributed to the clinical disease in these cases. Possible causes include a false positive IDT result in a dog with atopic-like dermatitis and additional unrecognized FIAD or environmental hypersensitivities. It is also currently unknown if dogs could develop auto-immunity to *Malassezia* allergen analogues as recognized in humans.⁴

In a nonpeer-reviewed report on *Malassezia* immunotherapy, results were reported as good to excellent in dogs treated with weekly injections of aqueous immunotherapy.¹⁶ Aluminium hydroxide (alum) is used as an adjuvant and a depot mediator in vaccines. Although aluminium promotes a Th2-response, unwanted in allergy therapy, the protective effect seems partly due to an enhanced allergen-specific IgG-production.^{20,21} In our study, we used alum-precipitated IT dosed as 1 mL subcutaneously every four weeks with dose adjustments in three cases. To the best of our knowledge, there are no studies comparing the efficacy of aqueous versus alum-precipitated IT in CAD. In humans, studies have failed to demonstrate differences in efficacy between various types of SCIT.^{22,23}

Atopic dogs are often poly-sensitized and combined sensitization to *Malassezia* and environmental allergens are common. Further assessment of whether these dogs would benefit from the addition of *Malassezia* extract to their treatment protocol compared to only using environmental allergens is needed. Previous studies have shown that mould proteases affect pollen extracts when mixed in the same aqueous SCIT.²⁴ However, one study showed a low protease activity in *Malassezia* extracts.²⁵ It is currently unknown if mixing fungal and other allergens affects the clinical outcome.

A major disadvantage of this study is the retrospective uncontrolled format and that a limited number of dogs fitted the inclusion criteria. A blinded, randomized controlled study of ASIT for *Malassezia* hypersensitivity, recording both clinical response as measured, for example, by

Canine Atopic Dermatitis Extent and Severity Index (CADESI) and PVAS, as well as serological changes in allergen-specific IgE and IgG, and changes in cytokines such as TGF- β and IL-10 reflecting immune tolerance, would be an interesting future study.

Based on the findings in this study, we conclude that SCIT appears to be a safe treatment for dogs with *Malassezia* hypersensitivity and that response to SCIT is similar to the effect reported using SCIT for dogs sensitized to other environmental allergens.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Appendix S1. Treatment administered to dogs pre- and post-Malassezia immunotherapy; response to immunotherapy in terms of clinical lesions and pruritus scores.

Résumé

Contexte – Il a été démontré que les réactions d'hypersensibilité à *Malassezia spp* se rencontrent chez les chiens atteints de dermatite atopique (AD) et entraînent une exacerbation des signes cliniques. L'amélioration des signes cliniques suivant un traitement antifongique est observé à la fois dans le syndrome de prolifération fongique et avec l'hypersensibilité à *Malassezia* (MHS). L'immunothérapie spécifique d'allergène sous-cutanée (SCIT) est considérée comme sûre et efficace pour le traitement de l'AD canine. Les effets secondaires sont considérés comme rares.

Objectifs – Décrire l'utilisation de la SCIT avec des extraits de *Malassezia* chez les chiens mono-sensibilisés.

Sujets – Seize chiens de propriétaires diagnostiqués avec MHS et traités à la SCIT.

Méthodes – Une revue rétrospective des données médicales des chiens atopiques diagnostiqués avec MHS, mono-sensibilisés aux allergènes de *Malassezia* aux tests intradermiques et traités par SCIT pendant plus de 10 mois. L'efficacité a été mesurée par utilisation dégressive d'anti-inflammatoires et d'antifongiques $\geq 50\%$ et par diminution du prurit $\geq 50\%$ tel qu'estimé par les propriétaires à l'aide d'un score de prurit.

Résultats – Une bonne réponse à la SCIT a été observée dans 9 des 16 cas (56%) avec une diminution à la fois de l'utilisation d'anti-inflammatoires et d'antifongiques ainsi qu'une diminution des scores de prurit $\geq 50\%$. Aucun effet indésirable n'a été rapporté.

Conclusion – L'immunothérapie spécifique d'allergène est un traitement sûr des chiens atteints d'hypersensibilité à *Malassezia*. L'efficacité de l'immunothérapie à *Malassezia* correspond bien aux résultats des études antérieures sur l'immunothérapie des allergènes environnementaux.

Resumen

Introducción – Se ha demostrado que las reacciones de hipersensibilidad a *Malassezia spp.* ocurren en perros con dermatitis atópica (AD) y causan exacerbación de los signos clínicos. La mejora de los signos clínicos después del uso de medicación antifúngica se observa tanto con el crecimiento excesivo de *Malassezia* como con la hipersensibilidad a *Malassezia* (MHS). La inmunoterapia subcutánea específica alérgica (SCIT) se considera un tratamiento seguro y eficaz para el tratamiento de la AD canine. Los efectos adversos se consideran raros.

Objetivos – Informar acerca del uso de SCIT con extractos de *Malassezia* en perros mono-sensibilizados.

Animales – Dieciséis perros de propietarios privados diagnosticados con MHS y tratados con SCIT.

Métodos – Revisión retrospectiva de los historiales médicos de perros atópicos diagnosticados con MHS, mono-sensibilizados para los alérgenos de *Malassezia* según la prueba intradérmica y tratados con SCIT durante más de 10 meses. La eficacia se midió por la disminución en el uso de medicación antiinflamatoria y antifúngica en $\geq 50\%$ y la disminución en el prurito en $\geq 50\%$ según la evaluación de los propietarios, usando una puntuación para prurito.

Resultados – Se observó una buena respuesta a SCIT en nueve de 16 casos (56%), con una reducción en el uso de medicación antiinflamatoria y antifúngica, así como una reducción en las puntuaciones de prurito $\geq 50\%$. No se observaron efectos adversos.

Conclusión – La inmunoterapia específica para alérgenos fue un tratamiento seguro para perros con hipersensibilidad a *Malassezia*. La eficacia de la inmunoterapia contra *Malassezia* corresponde bien con resultados de estudios previos de inmunoterapia para otros alérgenos ambientales.

Zusammenfassung

Hintergrund – Es konnte gezeigt werden, dass Hypersensibilitätsreaktionen auf *Malassezia spp.* bei Hunden mit atopischer Dermatitis (AD) vorkommen und eine Verschlimmerung klinischer Symptome verursachen. Eine Verbesserung der klinischen Symptome nach der Verwendung von Antimykotika konnte

sowohl bei Überwucherung durch *Malassezien*, wie auch bei Hypersensibilität auf *Malassezien* (MHS) gesehen werden. Die subkutane Allergen-spezifische Immuntherapie (SCIT) wird als sichere und effektive Behandlung beim Management der caninen AD betrachtet. Nebenwirkungen kommen selten vor.

Ziele – Ein Bericht über die Verwendung von SCIT mit *Malassezien*extrakt in mono-sensibilisierten Hunden.

Tiere – Sechzehn Hunde in Privatbesitz, die mit MHS diagnostiziert und mit SCIT behandelt worden waren.

Methoden – Es handelt sich um eine retrospektive Rückschau auf die medizinischen Daten von atopischen Hunden, die mit MHS diagnostiziert worden waren, mono-sensibilisiert waren auf *Malassezia* Allergene beim Intradermaltest und die mit SCIT länger als 10 Monate lang behandelt worden waren. Die Wirksamkeit wurde gemessen durch eine Verminderung der entzündungshemmenden und antimykotischen Behandlung von $\geq 50\%$ und durch eine Verminderung des Pruritus um $\geq 50\%$ nach dem Ermessen der BesitzerInnen, welche eine Juckreizskala verwendeten.

Ergebnisse – Eine gute Reaktion auf SCIT wurde in neun von 16 Fällen (56%) festgestellt, wobei sowohl eine Verminderung der entzündungshemmenden und antimykotischen Medikamente wie auch eine Verminderung der Juckreizwerte um $\geq 50\%$ erfolgte. Es wurden keine Nebenwirkungen beschrieben.

Schlussfolgerung – Die Allergen-spezifische Immuntherapie war eine sichere Behandlung für Hunde mit *Malassezia* Hypersensibilität. Die Wirksamkeit der *Malassezia* Immuntherapie korrelierte gut mit den Ergebnissen der vorhergehenden Studien über die Immuntherapie mit anderen Umgebungsallergenen.

要約

背景 – *Malassezia spp.*に対する過敏性反応は、アトピー性皮膚炎(AD)に罹患した犬において認められ、臨床徴候の悪化を引き起こすことが報告されている。マラセチアの過剰増殖またはマラセチア過敏症(MHS)の両方で、抗真菌薬の使用後の臨床症状の改善が認められる。皮下アレルゲン特異的免疫療法(SCIT)は、犬のADの管理のための安全かつ有効な治療法であり、有害事象はまれであると考えられている。

目的 – マラセチア単一感作犬に対するマラセチア抽出液を用いたSCITの使用報告をすること。

供与動物 – MHSと診断され、SCITで治療された16頭の飼い犬。

方法 – MHSと診断され、皮内試験でマラセチア抗原に対して単一感作され、10ヶ月以上SCITで治療されたアトピー犬の医療記録の回顧的調査を実施した。効能は、抗炎症薬および抗真菌薬の50%以上の減薬、飼い主によって評価される掻痒スコアによる50%以上の掻痒の減少によって評価した。

結果 – 抗炎症薬および抗真菌薬の使用と掻痒スコアの両方が50%以上減少したSCITに対する良好反応は、6症例中9症例(56%)で認められた。有害事象は報告されなかった。

結論 – アレルゲン特異的免疫療法はマラセチア過敏症の犬にとって安全な治療法であった。マラセチア免疫療法の有効性は、他の環境アレルゲンに対する免疫療法の過去の研究結果とよく一致していた。

摘要

背景 – 异位性皮膚炎(AD)患犬可能发生马拉色菌性超敏反应,从而加重临床症状。随着抗真菌药物的使用,马拉色菌过度增殖或马拉色菌过敏症(MHS)的临床症状可获得改善。皮下注射变应原特异性免疫治疗(SCIT)被认为是管理犬AD的一种安全有效的治疗方法。很少发生不良反应。

目的 – 报道SCIT在使用马拉色菌提取物单一致敏的犬上的应用。

动物 – 16只私家犬经诊断患有MHS,并使用SCIT进行治疗。

方法 – 回顾性分析诊断为MHS的异位性皮膚炎患犬的医疗记录,这些犬经皮内试验确定为马拉色菌变应原单一致敏,并使用SCIT治疗超过10个月。通过减少 $\geq 50\%$ 抗炎和抗真菌药物的使用和减少 $\geq 50\%$ 的搔痒程度来判定疗效,搔痒程度由动物主人根据搔痒得分进行评估。

结果 – 16只犬中有9只(56%)对SCIT产生良好反应,表现为抗炎和抗真菌药物的使用剂量减少,同时,搔痒得分降低 $\geq 50\%$ 。无不良反应报道。

结论 – 变应原特异性免疫治疗是一种治疗犬马拉色菌过敏症的安全方法。马拉色菌免疫治疗的疗效与以往其他环境过敏原免疫治疗的研究结果相一致。

Resumo

Contexto – Reações de hipersensibilidade à *Malassezia spp.* já tiveram a sua ocorrência demonstrada em cães com dermatite atópica (DA), assim como seu potencial de exacerbação dos sinais clínicos. A melhora dos sinais clínicos após a terapia antifúngica é observada tanto para o supercrescimento de *Malassezia* quanto para a hipersensibilidade à *Malassezia* (MHS). Imunoterapia alérgeno-específica subcutânea (SCIT) é considerada segura e eficaz no manejo da DA canina. Efeitos adversos são considerados raros.

Objetivos – Relatar o uso de SCIT com extratos de *Malassezia* em cães monossensibilizados.

Animais – Dezesesseis cães de proprietários diagnosticados com MHS e tratados com SCIT.

Métodos – Realizou-se um estudo retrospectivo do histórico de cães atópicos diagnosticados com MHS, monossensibilizados para alérgenos de *Malassezia* no teste intradérmico e tratados com SCIT por mais de 10 meses. A eficácia foi mensurada pela redução $\geq 50\%$ no uso de anti-inflamatórios e antifúngicos e pelo decréscimo $\geq 50\%$ no prurido avaliado pelos proprietários usando uma escala de prurido.

Resultados – Boa resposta ao SCIT foi observada em nove dos 16 pacientes (56%) com redução tanto do uso de anti-inflamatórios/antifúngicos quanto pela redução no escore de prurido $\geq 50\%$. Não foram observados efeitos colaterais.

Conclusão – A imunoterapia alérgeno-específica se mostrou um tratamento seguro para cães com hipersensibilidade à *Malassezia*. A eficácia da imunoterapia para *Malassezia* corrobora bem com os resultados de estudos anteriores de imunoterapia com outros alérgenos ambientais.

Appendix S1. Treatment administered to dogs pre-Malassezia immunotherapy; response to immunotherapy in terms of treatments administered and pruritus scores

CASE	PRE-SCIT TX	SCIT DOSE-ADJUSTMENT	POST-SCIT TX	POST-SCIT TX CHANGE SPECIFIED	>50 % LESS TX	PRE-SCIT PRURITUS SCORE IN RECORDS	POST-SCIT PRURITUS SCORE IN RECORDS	> 50 % LESS PRURITUS ASSESSED BY OWNERS	CONTINUED SCIT
1	Shampoo 2% chlorhexidine and 2% miconazole twice weekly. Betamethasone 1 mg/mL in ears twice weekly. Hydrocortisone aceponate 0.584 mg/mL topically twice weekly.	1 mL/ 3 weeks	Shampoo 2% chlorhexidine and 2% miconazole every other week. Betamethasone 1 mg/mL in ears twice weekly. Hydrocortisone aceponate 0.584 mg/mL every other week.	75% less antifungal shampoo and HAC No change in Betamethasone	Yes	NR	NR	Yes ²	Yes
2	Shampoo 2% chlorhexidine and 2% miconazole twice weekly. Hydrocortisone aceponate 0.584 mg/mL topically twice weekly. Methylprednisolone 0.2 mg/kg po eod.		Shampoo 2% chlorhexidine and 2% miconazole twice weekly. Hydrocortisone aceponate 0.584 mg/mL topically twice weekly. Methylprednisolone 0.2 mg/kg po eod.	No change	No	NR	NR	No ¹	Yes
3	Shampoo 2% chlorhexidine and 2% miconazole once weekly. Methylprednisolone po 0.25 mg/kg eod.	1 mL/3 weeks	Shampoo 2% chlorhexidine and 2% miconazole every other week.	50% less antifungal shampoo 100% less anti-inflammatory medication	Yes	NR	NR	Yes ¹	Yes
4	Shampoo 2% chlorhexidine and 2% miconazole twice weekly. Hydrocortisone aceponate 0.584 mg/mL topically twice weekly.		Shampoo 2% chlorhexidine and 2% miconazole twice weekly. Hydrocortisone aceponate 0.584 mg/mL topically twice weekly. Methylprednisolone 0.3 mg/kg po eod Ciclosporin 4 mg/kg po eod.	Antifungal shampoo unchanged Increased anti-inflammatory medication	No	NR	NR	No ¹	No
5	Shampoo 2% chlorhexidine and 2% miconazole twice weekly. Betamethasone 1 mg/mL in ears twice weekly. Hydrocortisone aceponate 0.584 mg/mL topically 2-3 times weekly.		Shampoo 2% chlorhexidine and 2% miconazole every other week. Hydrocortisone aceponate 0.584 mg/mL every other week.	75% less antifungal shampoo 80% less anti-inflammatory medication	Yes	4/10	1/10	Yes ²	Yes
6	Shampoo 2% chlorhexidine and 2% miconazole twice weekly. Hydrocortisone aceponate 0.584 mg/mL topically for flares. Cetirizine 0.4 mg/kg twice daily.	0.8 mL/ 3 weeks	Shampoo 2% chlorhexidine and 2% miconazole twice weekly. Ketoconazole 5 mg/kg twice weekly. Hydrocortisone aceponate 0.584 mg/mL topically once weekly. Cetirizine 1.2 mg/kg twice daily. Methylprednisolone 0.3 mg/kg twice daily 3-5 days every other month.	Antifungal shampoo unchanged Increased anti-inflammatory medication	No	NR	NR	No ¹	No
7	Shampoo 2% chlorhexidine and 2% miconazole once weekly. Betamethasone 1 mg/mL in ears once weekly. Hydrocortisone aceponate 0.584 mg/mL topically once-twice weekly Tacrolimus 0.1 % twice weekly for eyelids. Dexamethasone 1 mg/mL once daily for conjunctivitis.		Prednisolone pivalate 5 mg/g in eyes once monthly.	100% less antifungal shampoo > 90% less anti-inflammatory medication	Yes	6/10	NR	Yes ¹	Yes

8	Shampoo 2% chlorhexidine and 2% miconazole once weekly. Methylprednisolone 0.4 mg/kg po eod. Betamethasone 1 mg/mL in ears once weekly. Hydrocortisone aceponate 0.584 mg/mL topically once weekly.		Methylprednisolone 0.2 mg/kg po once monthly. Betamethasone 1 mg/mL in ears and Hydrocortisone aceponate 0.584 mg/mL topically 3 times a year.	100% less antifungal shampoo > 90% less anti-inflammatory medication	Yes	10/10	NR	Yes ¹	Yes
9	Shampoo 2% chlorhexidine and 2% miconazole once-twice weekly. Methylprednisolone 0.3 mg/kg eod Hydrocortisone aceponate 0.584 mg/mL topically twice weekly.		Shampoo 2% chlorhexidine and 2% miconazole once weekly. Methylprednisolone 0.3 mg/kg po eod Hydrocortisone aceponate 0.584 mg/mL topically twice weekly.	No change	No	NR	NR	No ¹	No
10	Shampoo 2% chlorhexidine and 2% miconazole once-twice weekly. Hydrocortisone aceponate 0.584 mg/mL topically twice weekly.		Shampoo 2% chlorhexidine and 2% miconazole once weekly. Methylprednisolone 0.3 mg/kg po eod. Ciclosporin po 3.4 mg/kg daily.	Antifungal shampoo unchanged Increased anti-inflammatory medication	No	8/10	NR	No ¹	No
11	Shampoo 2% chlorhexidine and 2% miconazole once-twice weekly. Betamethasone 1 mg/mL in ears once weekly. Hydrocortisone aceponate 0.584 mg/mL topically twice weekly.		Shampoo 2% chlorhexidine once weekly. Betamethasone 1 mg/mL in ears and Hydrocortisone aceponate 0.584 mg/mL twice monthly.	No change in antifungal shampoo 90% less anti-inflammatory medication	Yes	NR	NR	Yes ²	Yes
12	Hydrocortisone aceponate 0.584 mg/mL topically twice weekly.		Cetirizine 1 mg/kg po twice daily. Betamethasone 1 mg/mL in ears for monthly.	Increased anti-inflammatory medication	No	NR	NR	No ²	Yes
13	Shampoo 2% chlorhexidine and 2% miconazole once weekly. Betamethasone 1 mg/mL in ears once weekly. Hydrocortisone aceponate 0.584 mg/mL topically eod.		Shampoo 2% chlorhexidine and 2% miconazole and Betamethasone 1 mg/mL in ears once monthly. Hydrocortisone aceponate 0.584 mg/mL topically every two weeks.	75% less antifungal shampoo and Betamethasone 85% less HAC	Yes	NR	0/10	Yes ¹	Yes
14	Shampoo 2% chlorhexidine and 2% miconazole every two weeks. Hydrocortisone aceponate 0.584 mg/mL topically twice weekly.		Shampoo 2% chlorhexidine and 2% miconazole for every three weeks	60% less antifungal shampoo 100% less HAC	Yes	NR	NR	Yes ²	Yes
15	Shampoo 2% chlorhexidine and 2% miconazole 3-4 times weekly. Hydrocortisone aceponate 0.584 mg/mL 3-4 times weekly. Betamethasone 1 mg/mL in ears once weekly.		Shampoo 2% chlorhexidine and 2% miconazole 3-4 times weekly. Betamethasone 1 mg/mL in ears once weekly. Hydrocortisone aceponate 0.584 mg/mL 3-4 times weekly.	No change in antifungal or anti-inflammatory medication	No	NR	NR	No ²	No
16	Shampoo 2% chlorhexidine and 2% miconazole once weekly. Betamethasone 1 mg/mL in ears once weekly. Cetirizine 1 mg/kg twice daily.		Betamethasone 1 mg/mL in ears once monthly.	100% less antifungal shampoo and cetirizine 75% less Betamethasone	Yes	NR	NR	Yes ¹	Yes

Abbreviations: tx treatment; po per os; eod every other day; HAC Hydrocortisone Aceponate; NR not recorded; ¹Based on record notes; ²Based on telephone contact with owners; SCIT Sub-cutaneous immunotherapy