

Successful treatment of sebaceous adenitis in a rabbit with ciclosporin and triglycerides

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Conflict of Interest

No conflict of interest has been declared.

Abstract

A 4-year-old rabbit was presented with a chronic exfoliative dermatitis and patchy alopecia. General physical examination revealed no abnormalities. Skin scrapings and fungal culture were negative. A blood sample was obtained for a complete blood cell count and biochemical profile, and yielded results that were within normal limits. Radiographic examination of the thorax excluded the presence of a thymoma. Histopathology of the skin showed orthokeratotic hyperkeratosis, absence of sebaceous glands and mural lymphocytic folliculitis, consistent with sebaceous adenitis. Oral treatment was started with ciclosporin dissolved in a medium-chain triglyceride solution (Miglyol 812), combined with essential fatty acids and topical propylene glycol sprays. Within 2 months of treatment, complete regression of skin lesions and regrowth of hair was observed. Serum chemistry values including kidney and liver function tests remained within reference range during the course of treatment. Histopathological examination of control biopsies of the skin showed presence of normal sebaceous glands and active hair follicles. Treatment was changed to a different pharmaceutical formulation of ciclosporin without Miglyol and deterioration of clinical signs was noticed. Using pure Miglyol 812, however, resulted in a gradual improvement of 60%. A nearly complete response was again observed after re-administration of the combination ciclosporin/Miglyol. It is hypothesized that sebaceous adenitis in the rabbit is most likely due to an autoimmune reaction directed at the sebaceous glands and a defect

in lipid metabolism. The outcome indicates that a combination of ciclosporin and Miglyol 812 is a promising new treatment for sebaceous adenitis in rabbits.

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Introduction

Sebaceous adenitis is a skin disease reported in rabbits, aged from 2.5 to 7.5 years.¹ Clinical signs may include focal to gradually generalized exfoliative dermatitis and patchy alopecia without pruritus. Compatible histological findings include inflammation or an absence of sebaceous glands in combination with a mural lymphocytic folliculitis. These features are comparable with canine sebaceous adenitis.^{1,2} Various treatments for this disease in the rabbit have been described.¹ Thus far, treatment with isotretinoin, prednisolone and azathioprine have not led to significant improvement in clinical signs.¹ In dogs with sebaceous adenitis, ciclosporin has proved to be a promising new drug. In 12 dogs treated with ciclosporin, a significant improvement in clinical, histological and immunohistochemical signs was shown.² This case report describes the successful treatment of a rabbit with sebaceous adenitis using a combination of ciclosporin and triglycerides.

Case report

A 4-year-old male castrated rabbit with a bodyweight of 1.4 kg was presented with a 1.5-year history of chronic exfoliative dermatitis and patchy alopecia without pruritus. The rabbit was housed indoors with another, clinically healthy rabbit, but caged separately. Both rabbits were fed *ad libitum* hay, a variety of vegetables and a commercial rabbit pellet. Previous therapies with griseofulvin, ivermectin, marbofloxacin and selamectin had not improved the skin lesions. On referral, general physical examination revealed no abnormalities. On dermatological examination, scaling, erythema and alopecia were present on the head, dorsal neck, ventral thorax and abdomen, dorsum and hindlimbs. Follicular casts were present, especially on the ear margins (Figs 1 and 2). The rabbit showed a pain response when the skin was touched.

Differential diagnoses included dermatophytosis, *Malassezia* dermatitis, ectoparasitosis, epitheliotropic lymphoma, sebaceous adenitis, thymoma-associated exfoliative dermatitis and autoimmune hepatitis-associated exfoliative dermatitis.^{1,3,4} Skin scrapings and fungal culture were negative. A blood sample was obtained for a complete blood cell count and biochemical profile and yielded results that

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Figure 1. Rabbit with sebaceous adenitis. Note the follicular casts at the ear margins and multifocal areas of patchy alopecia.

were within normal limits, except for a mild elevation of alanine aminotransferase (Table 1).

Radiographic examination of the thorax excluded the presence of a thymoma. Skin biopsies for histopathological examination were obtained under general anaesthesia using isoflurane.

Considering the severity of the clinical signs, trial therapy was started with oral prednisone solution (1 mg kg^{-1} once daily), trimethoprim/sulfadiazine (27 mg kg^{-1} twice daily, Sulphatrim, ASTfarma, Oudewater, the Netherlands) for secondary bacterial infection, and fenbendazole (20 mg kg^{-1} once daily, Panacur, Intervet Nederland B.V., Boxmeer, The Netherlands) was added for prevention of an *Encephalitozoon cuniculi* infection. No improvement was seen after 14 days of treatment. Histological examination of the skin showed orthokeratotic hyperkeratosis, absence of sebaceous glands and mural lymphocytic folliculitis consistent with sebaceous adenitis (Fig. 3). The prednisone administration was tapered off over a 2-week duration, and treatment was changed to oral ciclosporin (5 mg kg^{-1} once daily, Neoral®, Novartis Animal Health, Breda, the Netherlands) dissolved in an equal amount of



Figure 2. Ventrum of rabbit. Note the alopecia and erythema.

Miglyol, a medium-chain triglyceride solution (Miglyol 812®, BUFA, Uitgeest, the Netherlands), combined with oral essential fatty acids given at the same time (0.5 mL once daily, Megaderm®, Virbac Animal Health, Barneveld, the Netherlands). In addition, topical propylene glycol sprays were applied to the skin. An initial improvement was noticeable after 3 weeks of treatment and within 2 months the skin lesions had completely resolved and the hair coat almost returned to normal (Fig. 4). The owner found the rabbit to be more active and it had gained 200 g of bodyweight. At that time, blood for a serum chemistry profile was obtained to monitor the effects of therapy on treatment (Table 1). Several changes in treatment were attempted to find the most effective and least costly treatment. Changes in treatment schedules were as follows.

Table 1. Biochemical blood profile (internal laboratory reference values) of the rabbit with sebaceous adenitis; (a) prior to treatment; (b) after 2 months of treatment with ciclosporin/Miglyol and essential fatty acids; (c) after 4 months of ciclosporin/Miglyol treatment, including different treatment schedules and (d) after treatment with ciclosporin and essential fatty acids, without Miglyol 812

	(a) Prior to treatment	(b) Treatment with ciclosporin/Miglyol and EFA: 2 months	(c) Treatment with ciclosporin/Miglyol and EFA: 4 months	(d) Treatment with ciclosporin and EFA	Reference values	Unit
Urea	6.6		6.4	5.4	5.2–9.6	mmol L^{-1}
Creatinine	124		108	128	69–128	$\mu\text{mol L}^{-1}$
Bile acids	7	4	2	3	4–25	$\mu\text{mol L}^{-1}$
Alkaline phosphatase			62	48	17–206	IU L^{-1}
Alanine aminotransferase	70	95	53	60	8–21	IU L^{-1}
Aspartate transaminase				42	15–39	IU L^{-1}
Total protein	64				54–69	g L^{-1}
Albumin	42				34.3–48.8	g L^{-1}

EFA, essential fatty acids.

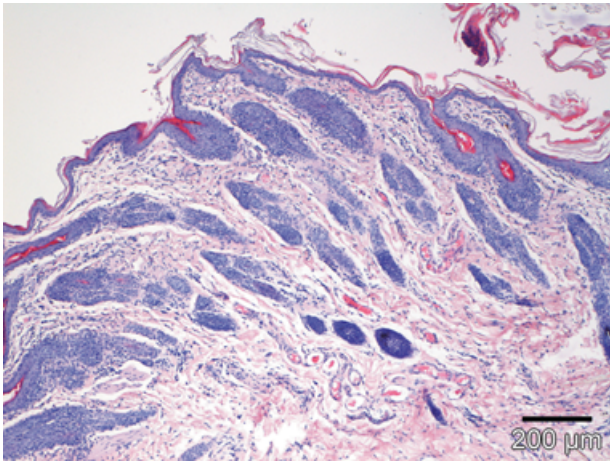


Figure 3. Photomicrograph of skin from the rabbit. Note the perifollicular lymphocytic folliculitis and absence of sebaceous glands (haematoxylin and eosin $\times 100$).



Figure 4. Rabbit 2 months after starting treatment with ciclosporin/Miglyol.

- 1 The administration of the ciclosporin/Miglyol solution was changed to every other day, with a continuation of daily fatty acids and propylene glycol sprays. This resulted in a relapse of mild clinical signs (patchy alopecia) within 3 weeks.
- 2 On daily administration, the dose of the ciclosporin/Miglyol solution was tapered to 2.5 mg kg^{-1} . This dosage, but also any other below 5 mg kg^{-1} , was found to be less effective. Within a period of 4 months, propylene glycol sprays were gradually eliminated from the treatment protocol without any deleterious effects. At this time, bile acids and kidney values were still within normal limits for rabbits. Repeat histopathological examination of skin biopsies taken from similar areas as before revealed normal small sebaceous glands and active hair follicles (Fig. 5).
- 3 Due to the high cost of the ciclosporin/Miglyol, treatment was changed to a different pharmaceutical formulation of ciclosporin without Miglyol (Atopica®, Novartis Animal Health) with continuation of the essential fatty acids. Deterioration of clinical signs was seen within 2 months on a daily dose of 6 mg kg^{-1} . Even a higher dosage (16 mg kg^{-1} once daily) given for another

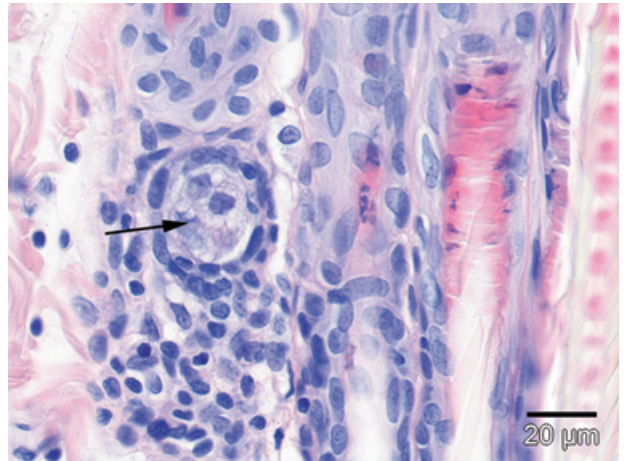


Figure 5. Photomicrograph of skin of the rabbit after two months of treatment with ciclosporin/Miglyol solution. Normal small sebaceous glands are shown (arrow) (haematoxylin and eosin $\times 400$).

3 weeks was ineffective. Within 3 weeks after re-administration of the ciclosporin/Miglyol combination, clinical improvement was seen again.

- 4 To determine the effect of Miglyol in this combination, ciclosporin was removed from the treatment protocol. The skin and haircoat gradually continued to improve during the next 7 weeks and a 60% maximum improvement of hair regrowth had been reached. No deterioration was noticed within 10 weeks of treatment. On readministration of the combination of CsA/Miglyol, again a complete remission of clinical signs was seen in an otherwise healthy rabbit.

Discussion

In this case report, successful treatment with a ciclosporin/Miglyol oral solution is described in a rabbit with chronic sebaceous adenitis. Sebaceous adenitis is a skin disease with an unknown aetiology. In certain dog breeds such as the akita and standard poodle, an autosomal recessive mode of inheritance has been identified.^{5,6} In the dog, leakage of sebum due to a primary defect in the structure of the sebaceous glands or ducts has been theorized to lead to a foreign body reaction.^{2,5} Another possibility in this species, is a defect in sebum production caused by an abnormal lipid metabolism.² Finally, immunohistology of canine skin with acute sebaceous adenitis has shown the presence of a T-cell mediated inflammatory reaction around the sebaceous duct and hair follicle, suggesting an immune-mediated pathogenesis.⁷ The latter is supported by the successful treatment of canine sebaceous adenitis with ciclosporin.² In rabbits, an exfoliative dermatitis with absence of sebaceous glands and a lymphocytic mural folliculitis has been described previously. In all of these cases an immune-mediated aetiology was suggested.^{1,3,4} In our study, complete remission of clinical signs and presence of normal sebaceous glands was only seen after treatment with a combination of ciclosporin and Miglyol, and not with ciclosporin alone.

Miglyols are synthetic neutral oils and are composed of multiple medium-chain triglycerides (MCT). The main advantage over long-chain triglycerides of MCT is their quick metabolization.⁸ Miglyol is used in pharmaceutical solutions, parenteral nutrition and cosmetics. It has mainly a carrier or solvent function and facilitates drug absorption. The difference in results between the treatment with ciclosporin and the combination solution of ciclosporin/Miglyol in this rabbit might be due to a facilitated intake of ciclosporin by Miglyol, because ciclosporin is a lipophilic cyclic polypeptide.⁹ However, it might also be due to an effect of Miglyol itself, especially since a gradual improvement, up to 60%, was present after treatment with Miglyol 812 alone. An explanation for these observations could be found in the fact that triglycerides are components of sebum in various species. Although they have been found to be predominant in human sebum, they are a minor component in other animals including the rabbit.¹⁰ Thus, the question remains whether or not it is the Miglyol 812 that corrects the abnormal lipid metabolism in lapine sebaceous adenitis and leads to improvement of sebum production. During the whole treatment trial, this rabbit had a daily intake of essential fatty acids. Without the supplementation of Miglyol, these fatty acids apparently had insufficient effect, which is in agreement with the results described by White et al.¹ Medium-chain triglycerides have a supporting effect on the efficient delivery of omega-3 fatty acids to tissues.¹¹ In addition, linolenic acid or linoleic acid might be able to enhance the solubility of ciclosporin in Miglyol by providing a lower pH when given simultaneously.

We conclude that the use of ciclosporin and Miglyol was safe in this rabbit, which is in accordance with other reports in rabbits and laboratory rodents.^{9,12,13} Further prospective studies with more animals are required to evaluate if the combination ciclosporin/Miglyol 812 could become a promising new therapy for this disease.

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Résumé Un lapin âgé de 4 ans a été présenté pour une dermatite chronique exfoliative associée à une alopecie multifocale. L'examen général n'a pas montré d'anomalie. Les raclages et cultures fongiques étaient négatifs. Une numération formule et une biochimie n'ont pas montré d'anomalie. L'examen radiographique du thorax a exclu la présence d'un thymome. L'histopathologie cutanée a montré une hyperkératose orthokératosique, une absence de glandes sébacées et une folliculite murale lymphocytaire, compatibles avec une adénite sébacée. Un traitement a été débuté avec de la ciclosporine orale, dissoute dans une solution de triglycérides (Miglyol 812), en association avec des acides gras essentiels et des sprays à base de propylène glycol. Après deux mois de traitement, une régression complète des lésions cutanées et une repousse pilaire a été notée. Les données biochimiques, notamment hépatiques et rénales, sont restées dans les normes pendant le traitement. L'histopathologie cutanée de biopsies de contrôle a montré la présence de glandes sébacées normales et de follicules pileux actifs. Le traitement a été modifié pour une formulation pharmaceutique de ciclosporine sans Miglyol et une détérioration des signes cliniques a été notée. En utilisant du Miglyol 812 pur, une amélioration d'environ 60 pour cent a été notée. Une réponse presque complète a été observée en remettant en place l'association ciclosporin/Miglyol. Il est proposé que l'adénite sébacée du lapin est une réaction auto-immune centrée sur la glande sébacée associée à un défaut du métabolisme lipidique. Ce cas indique que l'association de ciclosporine et de Miglyol 812 est un traitement prometteur de l'adénite sébacée du lapin.

Resumen Se presentó un conejo de 4 años de edad con dermatitis exfoliativa crónica y alopecia discontinua. El examen físico general no desveló anomalías. Raspados de la piel y cultivos fúngicos fueron

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negativos. Se obtuvo una muestra de sangre para un conteo total y perfil bioquímico con resultados dentro de los límites normales. El examen radiológico del tórax excluyó la presencia de timoma. La histopatología de la piel demostró ortoqueratosis hiperqueratótica, ausencia de glándulas sebáceas y folliculitis mural linfocítica consistente con adenitis sebácea. Se inició el tratamiento oral con ciclosporina disuelta en una solución de triglicéridos de cadena media (Miglyol 812), combinada con ácidos grasos esenciales y pulverización de propilenglicol por vía tópica. A los dos meses del tratamiento se observó regresión completa de las lesiones de la piel y crecimiento del pelo. El análisis bioquímico indicó valores normales en el hígado y riñón durante el tratamiento. El análisis histopatológico de biopsias control de la piel demostró la presencia de glándulas sebáceas normales y folículos pilosos activos. El tratamiento se cambió a una formulación diferente de ciclosporina sin Miglyol y se observó un deterioro en las lesiones. Utilizando Miglyol 812 puro, sin embargo, resultó en una mejora gradual del 60%. Una respuesta casi completa se observó de nuevo tras la readministración de la combinación ciclosporina/Miglyol. Nuestra hipótesis es que la adenitis sebácea en el conejo es probablemente debida a una reacción autoinmune dirigida frente a las glándulas sebáceas y a un defecto en el metabolismo lipídico. El resultado indica que la combinación de ciclosporina y Miglyol 812 es un nuevo tratamiento prometedor frente a la adenitis sebácea en conejos.

Zusammenfassung Ein vier Jahre altes Kaninchen wurde mit einer chronischen, exfoliativen Dermatitis und fleckiger Alopezie vorgestellt. Die allgemeine Untersuchung ergab keine Auffälligkeiten. Hautgeschabsel und Pilzkulturen waren negativ. Eine Blutprobe wurde für eine komplette Blutzellzählung und ein biochemisches Profil entnommen und lieferte Ergebnisse innerhalb der normalen Grenzwerte. Die Röntgenuntersuchung des Thorax schloss das Vorliegen eines Thymoms aus. Die Histopathologie der Haut zeigte orthokeratotische Hyperkeratose, Abwesenheit von Talgdrüsen und eine murale lymphozytäre Follikulitis, was mit einer Sebadenitis übereinstimmte. Eine orale Behandlung mit Cyclosporin, aufgelöst in einer mittel-kettigen Triglyzeridlösung (Miglyol 812), kombiniert mit essentiellen Fettsäuren und topischen Propylenglykolduschen wurde begonnen. Innerhalb von zwei Behandlungsmonaten wurde ein vollständiger Rückgang der Hautveränderungen und ein Wieder Wachstum der Haare beobachtet. Die Blutchemiewerte inklusive Nieren- und Leberfunktionstests blieben während der ganzen Behandlungsdauer innerhalb der Referenzwerte. Die histopathologische Untersuchung der Kontrollbiopsien der Haut zeigte das Vorhandensein von normalen Talgdrüsen und aktiven Haarfollikeln. Die Behandlung wurde umgestellt auf eine andere Formulierung des Cyclosporins (ohne Miglyol) und eine Verschlechterung der Symptomatik wurde bemerkt. Die Verwendung von reinem Miglyol 812 resultierte jedoch in einer graduellen Verbesserung von sechzig Prozent. Eine fast vollständige Reaktion wurde wiederum bei der neuerlichen Verabreichung der Kombination von Cyclosporin/Miglyol beobachtet. Es wird die Hypothese aufgestellt, dass die Sebadentitis bei Kaninchen auf einer Autoimmunreaktion, die auf die Talgdrüsen ausgerichtet ist, sowie auf einem Defekt im Fettstoffwechsel beruht. Das Ergebnis besagt, dass die Kombination von Cyclosporin und Miglyol 812 eine viel versprechende neue Behandlung für die Sebadentitis bei Kaninchen darstellt.