



Use of maropitant for the control of pruritus in non-flea, non-food-induced feline hypersensitivity dermatitis: an open-label uncontrolled pilot study

Journal of Feline Medicine and Surgery
1–6

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DOI: 10.1177/1098612X18811372

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Abstract

Objectives Non-flea, non-food-induced hypersensitivity dermatitis (NFNFIHD) is a common inflammatory and pruritic skin disease in cats. When avoidance and conventional systemic immunosuppressive treatments fail to control the clinical signs, there are limited treatment options. The aim of this study was to evaluate the efficacy and tolerability of maropitant in feline NFNFIHD.

Methods In an open-label uncontrolled study, cats with proven non-seasonal NFNFIHD were treated with maropitant 2 mg/kg PO q24h daily for 4 weeks. Clinical lesions were evaluated with the Scoring Feline Allergic Dermatitis (SCORFAD) system and pruritus was evaluated with a 10 cm visual analogue scale (VAS) before and at the end of the study. Owners assessed global efficacy and tolerability with a 4-point scale at the end of the study. Adverse events and body weight changes were recorded.

Results Twelve cats were treated with a mean initial maropitant dose of 2.22 mg/kg PO q24h. The treatment decreased both SCORFAD and pruritus VAS (pVAS) scores in all cats except one, in which only pruritus was reduced. The efficacy and the tolerability of the treatment were judged as excellent or good by 83.3% of owners. Treatment did not cause any side effects other than, in few cases, short-time, self-limiting sialorrhoea.

Conclusions and clinical relevance Maropitant seems to be an effective, well-tolerated therapeutic option to control pruritus in cats. Caution is needed in interpreting the results as the pVAS score system has not yet been validated in cats and the trial was uncontrolled. A further controlled study is required to confirm our findings.

Keywords: Maropitant; hypersensitivity; NK-1 receptor antagonist; atopic dermatitis treatment

Accepted: 15 October 2018

Introduction

Non-flea, non-food-induced feline hypersensitivity dermatitis (NFNFIHD) is a common disease in cats and its management can be challenging.^{1,2} There is limited evidence on the efficacy of immunotherapy and many cases are treated pharmacologically for the control of pruritus and skin lesions. The use of antihistamines, essential fatty acids, palmitoylethanolamide, glucocorticoids, ciclosporin and oclacitinib has been reported.^{3–9} However, in some cases, these therapies are ineffective, associated with excessive side effects, or unsuitable, and there is great need for other effective and safe drugs for the treatment of feline NFNFIHD.

Maropitant is an neurokinine-1 receptor (NK-1R) antagonist, which is registered for the prevention of

emesis and motion sickness in cats. Substance P (SP), a pruritogenic neurokinine, interacts with NK-1R and its action could be inhibited by maropitant.¹⁰ Aprepitant, an

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antiemetic with an NK-1R antagonist similar to maropitant, was effectively used to reduce pruritus due to various cutaneous and systemic causes in humans.^{11,12}

Our hypothesis was that maropitant could effectively decrease pruritus and skin lesions in cats with non-seasonal NFNFIHD. The goal of this pilot study was to assess the efficacy and tolerability of maropitant in the treatment of non-seasonal NFNFIHD.

Materials and methods

Animals

Client-owned cats with non-seasonal NFNFIHD were recruited by a board-certified veterinary dermatologist in three different clinics in Northern Italy. Signed informed consent was obtained from all owners. Diagnosis was based on clinical examination, exclusion of other pruritic dermatoses and fulfilment of Favrot's criteria for feline NFNFIHD.² In order to exclude flea infestation, all cats received spot-on imidacloprid for a minimum of 3 months (Advantage; Bayer), together with an environmental flea control (Solfact plus automatic casa [ciflutrin and piriproxifen]; Bayer). Secondary infections, when present, were treated with topical and/or systemic antibiotics and/or antifungal therapy prior to inclusion. To rule out adverse food reactions, a home-cooked or commercial diet, based on novel protein sources, or a hydrolysed food was fed exclusively for at least 8 weeks.

Cats having received long-acting injectable corticosteroids in the previous 4 weeks were not included. Two categories of patients were selected for this pilot study, representing possible indications of maropitant in the field: cats affected by concurrent diseases, which could not be treated with classical immunomodulating/immunosuppressive drugs, and cats not or only partially responding to ciclosporin or prednisolone. For the latter category cats were included only if the antipruritic treatment had been administered for at least 2 months. These treatments were continued during the trial and no dose changes were allowed. During the trial, no dietary, environmental or lifestyle changes were allowed.

Treatment

Maropitant was administered at 2 mg/kg PO q24h, for 4 weeks.

Evaluation of clinical efficacy

Primary outcomes were improvement of clinical lesions and of pruritus, which were evaluated at inclusion (V1) and after 4 weeks (V2) of maropitant treatment. Pruritus was measured by owners with a 10 cm visual analogue scale (pVAS) with word descriptors adapted from the dogs.^{13,14} Clinical lesions were assessed by the investigator using the validated scale Scoring Feline Allergic Dermatitis (SCORFAD; range 0–16).¹⁵ A secondary

outcome was the owner's evaluation of global efficacy at week 4 (V2), using a 0–3 scale (0 = poor, 1 = fair, 2 = good, 3 = excellent). Owing to the low number of cases and the open design of the study, no statistical analysis was performed.

Evaluation of tolerability

Cats were rechecked and weighed at V1 and V2, and every adverse event was recorded. Tolerability was rated by the owner on V2 on a 0–3 scale (0 = poor, 1 = fair, 2 = good, 3 = excellent) as previously described.⁴

Results

Animals

Twelve cats were included and none was prematurely withdrawn. Signalment data are summarised in Table 1. There were seven females (six spayed) and five castrated male cats. There were nine domestic shorthairs, one Birman, one Persian and one Chartreux cat. Mean body weight was 4.8 kg (range 3.7–6.2 kg). Mean age was 5.6 years (range 1–10 years). Two cats were feline immunodeficiency virus-positive and one was calicivirus-positive. One cat presented corpora nigra in the right eye. Clinical reaction patterns at the time of the inclusion, previous treatments and their responses, and concurrent treatments for each cat are also detailed in Table 1. Maropitant was administered at a mean dosage of 2.22 mg/kg per day (range 1.90–2.40 mg/kg).

Evaluation of clinical efficacy

The SCORFAD and pVAS scores at V1 and V2 are given in Table 1. The mean $\pm$ SD pVAS scores before and after treatment were 7.79 ± 1.72 and 2.15 ± 2.14 , respectively. Mean $\pm$ SD SCORFAD scores before and after treatment were 7.08 ± 2.27 and 2.25 ± 1.42 , respectively. Mean $\pm$ SD percentage reduction of pVAS was $72.80 \pm 22.02\%$ and $63.49 \pm 29.75\%$ for the SCORFAD.

The majority of the cats (91.7%) treated with maropitant showed improvement in both SCORFAD and pVAS scores (Figure 1). For cat 2, only pruritus improved.

There was no apparent difference in the outcome between cats receiving concurrent treatments and those that did not, as the mean $\pm$ SD pruritus score decreased from 7 ± 2.24 to 2.2 ± 1.48 and from 6.48 ± 1.21 to 1.58 ± 1.04 , respectively.

The general efficacy of the treatment was judged as excellent by seven (58.3%), as good by three (25%) and fair by two (16.7%) owners (Figure 1). None (0%) of the owners judged the treatment as poor. PVAS, SCORFAD and efficacy improvements for each cat are reported in Table 1.

Adverse events

Treatment was not associated with any change in weight. Two cats (cases 10 and 12) showed increased salivation

Table 1 Signalment, reaction patterns, previous and concurrent treatments, concurrent diseases and outcome of 12 cats with non-seasonal, non-flea, non-food-induced feline hypersensitivity dermatitis treated with maropitant

Number	Breed	Sex	Age (years)	Reaction pattern V1	Concurrent diseases	Previous treatment	Response to previous treatments	Concurrent treatments	Weight V1 (kg)	Weight V2 (kg)	SCORFAD V1	SCORFAD V2	V1 pVAS	V2 pVAS	Side effects	V2 tolerability	V2 efficacy
1	DSH	MC	8	E, A	FIV	OC; CSA	None; fair	–	5.7	6	7	0	10	0	–	3	3
2	Birman	F	3	EO, A	–	OC	Fair	OC	4	4	4	4	7.4	3	–	3	1
3	DSH	FS	1	E, EO	–	MP; CSA; OC	Good; fair,* fair	OC	3.7	3.9	10	2	5.4	0.4	–	3	3
4	DSH	MC	8	E, EO, A	FIV	MP; PEA-um; CSA	Good; fair; none	–	4.6	4.6	10	2	9.4	1.3	–	3	3
5	DSH	MC	7	E, EO, A	CN	BM; OC	Good; none	–	5	5	6	2	9.6	2	–	3	3
6	DSH	FS	8	E, A	–	MP; CSA	Good; none	–	5	5	6	2	6.5	1.8	–	3	3
7	DSH	FS	2	E, EO, A	–	CSA; OC	Good,* fair	OC	3.8	4	8	3	7.7	0.9	–	3	2
8	Persian	FS	10	E	CV	MP	Good	–	4.8	4.8	4	2	8.4	2.5	–	2	2
9	DSH	MC	3	EO, A	–	MP	Good	MP	6.2	6.2	7	0	6.9	1.4	–	3	3
10	DSH	FS	2	E, EO, A	–	–	–	–	4.2	4.2	11	3	7.2	1.9	SH	1	3
11	DSH	FS	7	MI, EO	–	CSA	Fair	CSA	5	5	6	2	5	2.2	–	3	2
12	Chartreux	MC	8	EO, A	–	–	–	–	5	4.9	6	5	10	8.4	SH	1	1

*Associated with side effects

V1 = visit 1 (day 1 of treatment); V2 = visit 2 (4 weeks of treatment); SCORFAD = Scoring Feline Allergic Dermatitis; pVAS = pruritus visual analogue scale; DSH = domestic shorthair; MC = male castrated; E = head and neck excoriations; A = symmetrical self-induced alopecia; FIV = feline immunodeficiency virus; OC = oclacitinib; CSA = ciclosporin; F = intact female; EO = eosinophilic dermatitis; FS = female spayed; MP = methylprednisolone; PEA-um = oral ultra-micronised palmitoylethanolamide; CN = corpora nigra; BM = betamethasone; CV = calicivirus; SH = sialorrhoea; MI = miliary dermatitis

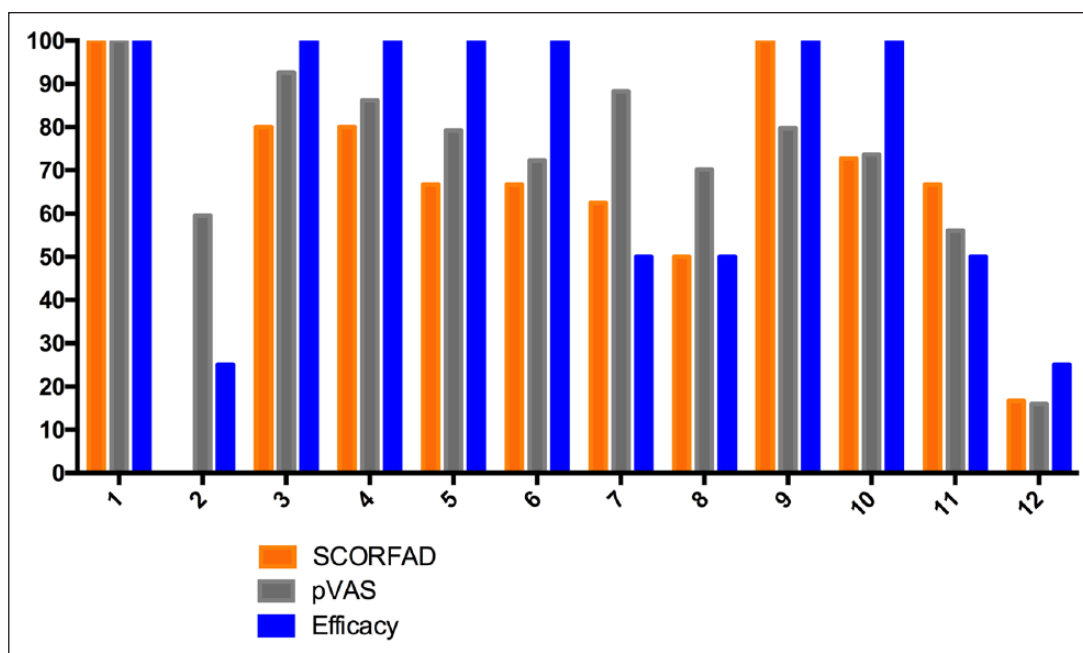


Figure 1 Percentage reduction in Scoring Feline Allergic Dermatitis (SCORFAD), pruritus visual analogue scale (pVAS) and efficacy scores after the treatment in 12 included cats

for a few minutes after each tablet administration. No other adverse events were recorded. The tolerability was judged as excellent by nine owners (75%), as good by one (8.3%) and fair by two (16.7%).

Discussion

This is the first study to report the effective use maropitant in cats with NFNFIHD.

This was an open-label, uncontrolled pilot study with a small sample size, including cats with concurrent illnesses or taking antipruritic treatments that may complicate the interpretation of the results. Notwithstanding these limitations, maropitant seems to be effective in decreasing pruritus and clinical signs of feline allergy, and results appear comparable to those obtained with other antipruritic drugs, such as ciclosporin, corticosteroids and oclacitinib.^{16–18}

We believe that these preliminary data are interesting and worth being confirmed in a future randomised blinded controlled trial.

The mechanism of the antipruritic and anti-inflammatory effect of maropitant, an NK-1 antagonist, could rely on its ability to inhibit SP binding to its receptor. NK-1R is expressed by many cells, including cutaneous nerve-ending cells, keratinocytes and immune cells. SP has acute proinflammatory properties by inducing degranulation of mast cells and eosinophils and is involved in chronic pruritus by promoting the increase of sensory nerve fibres.^{19–21} The cutaneous pruritogenic effect of SP was demonstrated in humans by observing that intradermal injections of SP in healthy volunteers

evoked wheals, flare reaction and pruritus at the injection site.^{13,21,22} Serum levels of SP were reported to be increased in patients with atopic dermatitis and to correlate with itch intensity.²³ Furthermore, SP and its receptors were demonstrated in the epidermis of human atopic patients, but not in healthy individuals, and atopic patients were found to have an increase of SP-positive nerve fibres in skin lesions.^{24,25}

Unfortunately, little information is available on the role of SP in pruritus in pets. SP concentrations in the skin were assessed in both lesional and non-lesional skin of atopic dogs.²⁶ Surprisingly, lesional skin appeared to have less SP than non-lesional skin, maybe owing to the presence of inflammatory cytokines, which may have upregulated neuropeptide-specific peptidases. Furthermore, in the same study, capsaicin, a SP depletor, did not provide improvement of signs of atopic dermatitis in atopic dogs. In our study, performed in cats, both owners and investigators agreed on the clinical efficacy of maropitant. This difference could be due to a more crucial role of SP on pruritus in cats than in dogs. In fact, in the experience of the authors, the use of maropitant for the control of pruritus in dogs was disappointing.

Recently, two placebo-controlled, crossover studies were published reporting the use of maropitant in an experimental model of feline asthma. In these studies, maropitant was injected subcutaneously as a single dose (2 mg/kg) or administered orally (2 mg/kg) every other day for 28 days, respectively.^{27,28} Contrary to our findings, both studies reported maropitant failure for feline asthma. A reasonable explanation is that the tachykinin

receptors in the airway smooth muscles are predominantly NK-2, whereas those in the skin are mainly NK-1.^{29,30} SP interacts with NK-1R and maropitant is highly specific for NK-1R, which could explain the good results obtained in our study. In accordance with this hypothesis, the administration of the NK-1R antagonist BIIF 1149 CL significantly inhibited scratching behaviour in an atopic dermatitis mouse model.³¹

Although no blood analyses were performed in these patients, maropitant at 2 mg/kg PO q24h for 28 consecutive days seems to be well tolerated in cats, in accordance with previous studies.^{27,32,33} Maropitant is available as injectable solution for cats and the recommended dosage of 1 mg/kg q24h for up to 5 consecutive days. The daily dosage of 2 mg/kg chosen in our study followed a previous study and allowed a better oral administration.³³ For practical reasons, administration of tablets was preferred over the injectable solution for the 4 week treatment course. The only side effect we observed in this study was increased salivation in 2/12 cats, in accordance with a safety study in which maropitant was administered at different dosages (from 0–5 mg/kg) subcutaneously daily for 15 days, with no adverse signs, except sialorrhoea, in 1/30 cats.³³ We must emphasise that although chronic administration (up to 28 days every other day) of maropitant has already been reported in the literature, this was the first study to use maropitant at 2 mg/kg q24h over a period of 4 weeks, which is far beyond the registered dose in cats.^{18,28} Veterinarians should be well aware that this is an off-label indication and posology and that cats should be closely monitored for side effects when prescribing maropitant with this protocol.

In some cats maropitant was used with concomitant antipruritic medications (methylprednisolone or ciclosporin), which may have biased the results. Maropitant stimulates the production of cytochrome P450 3A4 isoform and consequently could have increased prednisolone or ciclosporin blood concentrations and decreased their clearance. However, the impact of this factor appears to be limited, as there was no apparent difference in the outcomes between cats receiving concurrent treatment and those that did not. Finally, it may be argued that pVAS score is not validated for cats, even if it was used in several studies in the past.^{4,34} The reader should interpret these results with caution and be aware that there are no good alternative ways to assess pruritus in cats at the moment.

Conclusions

Maropitant could be a treatment option for cats with NFNFIHD, particularly when other immunomodulating/immunosuppressive therapies are contraindicated or ineffective. More studies are needed to confirm this observation and to assess the safety of maropitant when administered as long-term maintenance therapy in cats.

Acknowledgements The authors thank Chiara Noli and Bert Devriendt for critically reviewing the manuscript.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding The authors received no financial support for the research, authorship, and/or publication of this article.

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