https://doi.org/10.17221/136/2021-VETMED

Clinical efficacy of membrane-free stem cell extracts for the treatment of canine atopic dermatitis

Young Sil Kim[1], Sang Eun Ha[3], Hyeona Bae[2], Dongbin Lee[2], DoHyeon Yu[2], Gon Sup Kim[3]**

[1]*T-stem Co., Ltd., Changwon, Gyeongsangnam-do, Republic of Korea*
[2]*College of Veterinary Medicine, Gyeongsang National University, Jinju-daero, Jinju, Republic of Korea*
[3]*Research Institute of Life Science and College of Veterinary Medicine, Gyeongsang National University, Jinju-daero, Jinju, Republic of Korea*

**Corresponding authors: yudh@gnu.ac.kr, gonskim@gnu.ac.kr*

Citation: Kim YS, Ha SE, Bae H, Lee D, Yu DH, Kim GS (2022): Clinical efficacy of membrane-free stem cell extracts for the treatment of canine atopic dermatitis. Vet Med-Czech 67, 463–470.

Abstract: Despite various treatment options for canine atopic dermatitis (cAD), therapeutic limitations still exist, including adverse effects and low absorption ratios. This study evaluated the effects of a membrane-free stem cell extract (MFSCE) on the clinical signs of atopic dogs. Thirty client-owned dogs previously diagnosed with cAD were separated into placebo (n = 10) and MFSCE-treated groups (n = 20). The dogs were treated with a cream (MFSCE and placebo) via dermal administration twice daily for 14 days, and the clinical response was recorded on days 0, 7, and 14. The MFSCE-treated group showed significantly decreased severity of pruritus on day 14 compared to that on day 0. In addition, the erythema, pigmentation, skin dryness, and thickness were remarkably decreased in the MFSCE-treated group on day 14 compared to those on day 0 whereas no significant changes were observed in the placebo-treated group. No general clinical signs or adverse effects were observed in this study. These results suggest that MFSCE could be a surrogate treatment option for cAD.

Keywords: atopic dermatitis; canine; clinical trial; membrane-free stem cell extract (MFSCE); veterinary medicine

Canine atopic dermatitis (cAD), a common skin disorder manifesting as chronic inflammation resulting from genetic and environmental factors, is becoming increasingly prevalent (Marsella 2021). Atopic dermatitis is accompanied by various clinical symptoms. Pruritus and erythema are the primary clinical signs, while hyperpigmentation and lichenification are secondary clinical signs (El Hachem et al. 2020). These clinical signs may be accompanied by self-trauma. Various indices or scales are used to classify the severity of cAD, including the canine atopic dermatitis extent and severity index (CADESI) and pruritus visual analogue scale (PVAS) (Cosgrove et al. 2013). CADESI is the most commonly used index and is calculated based on the severity of the lichenification and erythema at various body sites (Olivry et al. 2014). However, as CADESI does not include a pruritus scale, an additional scale for pruritus was used. Pruritus has various causes, such as skin barrier disruption, immunological disorders, and central/peripheral neural abnormalities (El Hachem et al. 2020).

Although various treatments, including glucocorticoids, cyclosporin, and oclacitinib, are used for symptom relief (Forsythe and Paterson 2014; Gonzales et al. 2014), these are limited by adverse effects (Santoro 2019). Many studies have been conducted to develop alternative products with

https://doi.org/10.17221/136/2021-VETMED

enhanced efficacy and safety (Daltro et al. 2020; Wu et al. 2021).

Stem cells, defined as undifferentiated and multipotent cells, are a new therapeutic target for various diseases owing to their potential efficacy for differentiation and regeneration in the body (Lee et al. 2012). Among stem cells, human adipose-derived stem cells (ADSCs) have received attention for their characteristic advantages, including the same properties as bone marrow stem cells, their accessibility and abundance compared to other stem cells (Kern et al. 2006). Recent studies have reported the anti-inflammatory, immunomodulatory, angiogenic, and wound healing effects of ADSCs (Lu et al. 2019) in addition to their anti-allergic effects (Jee et al. 2013). However, the limitations in using ADSCs as therapeutics include a low engraftment ratio, oncogenic possibility, immune rejection, non-specific differentiation, and short half-life (Marks et al. 2017). Various studies have been conducted to overcome these limitations (Kim and Park 2017).

A membrane-free stem cell extract (MFSCE), which includes 252 peptides from membrane-removed ADSCs, was developed using a patented technology to overcome the disadvantages of ADSCs (Venkatarame Gowda Saralamma et al. 2019). In a previous study, the total protein profile was identified using a liquid chromatography mass spectrometry (LC-MS) analysis, and the protein-protein interaction was identified using the Search Tool for the Retrieval of Interacting Genes (STRING) database (Venkatarame Gowda Saralamma et al. 2019). MFSCE contains 9 proteins, which are related to the inflammatory response, and 36 proteins, which are related to the wound healing. Furthermore, integrin (ITGB1) and annexin A1 (ANXA1) are included in MFSCE, which have anti-inflammatory effects via inhibiting the cytokine release in the macrophages (Venkatarame Gowda Saralamma et al. 2019). We also demonstrated the anti-inflammatory effect of MFSCE in lipopolysaccharide (LPS)-induced RAW264.7 cells (Venkatarame Gowda Saralamma et al. 2019). Moreover, MFSCE also inhibited interleukin-1alpha (IL-1α)-stimulated inflammation in rat primary chondrocytes (Lee et al. 2019). However, the anti-cAD effects of MFSCE in animals have not yet been reported. Thus, the present study evaluated the clinical effects of MFSCE on cAD. The clinical responses, as well as the general signs and symptoms of cAD, were also studied to determine the adverse effects of MFSCE.

MATERIAL AND METHODS

Experimental design

This was a placebo-controlled clinical trial. All the owners signed an informed consent form for clinical trials before enrolling their animals in the study.

Experimental procedures

STEM CELL COLLECTION AND MANIPULATION

The MFSCE from human ADSCs was provided by T-Stem Co., Ltd. (Changwon, Republic of Korea) as previously described (Park et al. 2021). Stem cells from healthy females in their twenties were separated, purified, and cultured in an incubator with 5% CO_2 at 37 °C. The donors underwent blood tests to check compatibility according to the Korean Food and Drug Administration. The cells were sub-cultured and extracted at passages 5–7. The cells were collected and their membranes were removed by ultrasonication and centrifugation. The supernatant was then filtered to collect the peptides. The non-toxicity of the MFSCE, the final product, was identified via nine safety tests performed by the Good Laboratory Practice accreditation authority.

MFSCE TREATMENT TO PARTICIPANTS ACCORDING TO THE GROUP

This randomised, blind, placebo control study included 30 dogs with spontaneous mild to moderate cAD. The cAD diagnosis was based on published guidelines (Hillier et al. 2014) and any dogs with a history of corticosteroid or cyclosporin treatments within 4 weeks of the experiment were excluded. The dogs were randomly assigned to treatment groups receiving the MFSCE (n = 20) or placebo (n = 10). The MFSCE-treated group was administered 3.5 ml of cream containing 5% of MFSCE and 95% of an additive [water (56.2%), glycerine (7%), caprylic/capric triglyceride (5%), propanediol (5%), shea butter (3%), niacinamide (2%), and other 29 ingredients (less than 2%)], while the placebo group was administered 3.5 ml of a cream consisting of 100% the additive. Each dog was treated

https://doi.org/10.17221/136/2021-VETMED

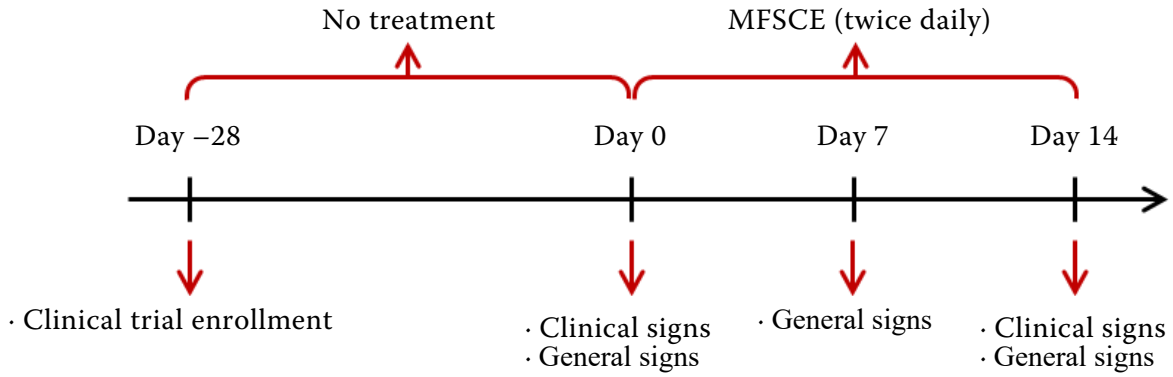

Figure 1. Study timeline of the MFSCE treatment and the assessment of the clinical and general signs
MFSCE = membrane-free stem cell extract

with a cream (placebo or the MFSCE) via dermal administration twice daily for 14 days. To evaluate the symptoms, the dogs with their owners visited the hospital on days 0, 7, and 14. The overall study timeline is shown in Figure 1.

EVALUATION OF CLINICAL EFFICACY

The clinical efficacy of cAD was evaluated based on five categories: pruritus, erythema, pigmentation, dryness, and change in skin thickness.

The pruritus score was based on five behavioural indices: 0 – no pruritus at the lesion with comfortable behaviour; 1 – apparent pruritus at the lesion with comfortable behaviour; 2 – slight scratching of the lesion with uncomfortable behaviour; 3 – severe scratching of the lesion with uncomfortable behaviour; and 4 – severe scratching of the lesion, lesion bleeding, and uncomfortable behaviour.

The erythema score was evaluated according to the presence of five symptoms at the lesion: 0 – no erythema; 1 – no erythema, but a slight colour change; 2 – slight erythema; 3 – moderate erythema; and 4 – severe erythema.

The pigmentation score was based on the evaluation of five lesion symptoms: 0 – no pigmentation; 1 – no pigmentation, but a slight colour change; 2 – slight pigmentation; 3 – moderate pigmentation; and 4 – severe pigmentation.

The dryness score was evaluated according to five lesion symptoms and behavioural indices: 0 – no skin dryness; 1 – dryness without corneous exfoliation; 2 – no corneal exfoliation with pruritus behaviour; 3 – corneous exfoliation with pruritus behaviour; and 4 – severe corneous exfoliation with pruritus behaviour.

Finally, the skin thickness score was evaluated based on five lesion symptoms and behavioural indices: 0 – soft skin without increased skin thickness; 1 – rough skin without increased skin thickness; 2 – rough skin with other symptoms such as pruritus, dryness, erythema, or pigmentation; 3 – increased skin thickness with other symptoms such as pruritus, dryness, erythema, or pigmentation; and 4 – severely increased skin thickness with other severe symptoms such as pruritus, dryness, erythema, or pigmentation.

The adverse effects were evaluated by observing the general symptoms. The general symptoms and scores are shown in Table 1. The progress of the

Table 1. General behavioural evaluation criteria to evaluate the adverse effect in dogs

Score	Clinical sign
1	Anorexia
1	Ocular discharge
1	Other skin disease in an area unrelated to the lesion
1	Alopecia in an area unrelated to the lesion
1	Nasal discharge
2	Fever
2	Abnormalities of urination and defecation
3	Abnormalities of respiration
4	Inability to walk
5	Inability to stand
10	Death
Total score	Clinical sign
0–5	Study continuation
6–9	Consider stopping the study
≥ 10	Study cessation

https://doi.org/10.17221/136/2021-VETMED

study was determined according to the general symptom scores: 0–5, study continuation; 6–9, consideration of stopping the study; and ≥ 10, study cessation.

Statistical analysis

The statistical analysis was performed using GraphPad Prism v2.00 (GraphPad Software, USA). All the data are expressed as the mean ± standard deviation.

Both groups were compared using paired Student's *t*-tests. Significance defined as $P < 0.05$.

RESULTS

MFSCE effect on pruritus

The pruritus score of the MFSCE-treated group decreased significantly after 14 days of treatment (0.90 ± 0.85) compared to that at day 0 (3.15 ± 0.75, $P < 0.05$), while no changes were observed in the placebo group (2.50 ± 0.53 at day 0 and 2.10 ± 0.88 at day 14) (Figure 2A).

MFSCE effect on erythema and pigmentation

The erythema score of the MFSCE-treated group decreased significantly after 14 days of treatment (1.05 ± 0.76) compared to that at day 0 (2.80 ± 0.77, $P < 0.05$), while no changes were observed in the placebo group (2.10 ± 0.74 at day 0 day and 2.30 ± 0.82 at day 14) (Figure 2B). The pigmentation score of the MFSCE-treated group also decreased significantly after 14 days of treatment (1.25 ± 0.97) compared to that at day 0 (2.70 ± 0.80, $P < 0.05$), while no changes were observed in the placebo group (1.50 ± 0.71 at day 0 and 1.50 ± 0.71 at day 14) (Figure 2C).

MFSCE effect on anti-dryness and skin thickness

The dryness score of the MFSCE-treated group decreased significantly after 14 days of treatment (1.15 ± 0.93) compared to that at day 0 (3.35 ± 0.67, $P < 0.05$), while no changes were observed in the placebo group (2.50 ± 1.27 at day 0 and 2.70 ± 1.06 at day 14) (Figure 2D). The skin thickness score

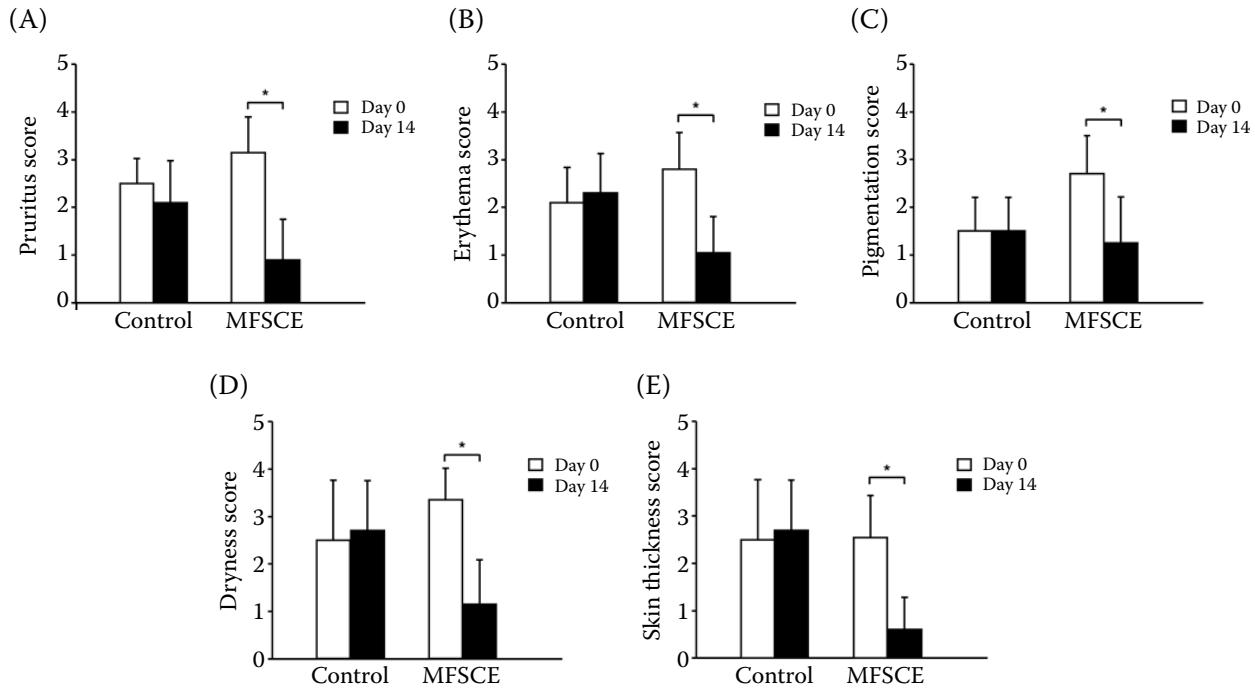

Figure 2. Changes in the clinical scores after the membrane-free stem cell extract (MFSCE) treatment

The placebo or MFSCE treatment was administered dermally twice daily for 14 days (placebo: $n = 10$; MFSCE: $n = 20$); The data are expressed as the mean ± standard deviation of the mean

*$P < 0.05$

https://doi.org/10.17221/136/2021-VETMED

of the MFSCE-treated group decreased significantly after 14 days of treatment (0.60 ± 0.68) compared to that at day 0 (2.55 ± 0.89, $P < 0.05$), while no changes were observed in the placebo group (2.50 ± 1.27 at day 0 and 2.70 ± 1.06 at day 14) (Figure 2E). No adverse effects were observed in any of the dogs included in this study (data not shown).

DISCUSSION

This is the first study to demonstrate the treatment effect of MFSCE on cAD without adverse effects in dogs. All the clinical signs related to cAD, including pruritus, erythema, pigmentation, dryness, and increased skin thickness, were significantly improved after 14 days of treatment. No changes in the general symptoms were observed during this period; thus, MFSCE had no adverse effects.

Among the various treatments used for cAD, topical treatments such as ointments, creams, or lotions are commonly used (Ference and Last 2009) due to the adverse effects of systemic treatments despite their excellent efficacy (Nuttall 2020). Although topical glucocorticoids (TGCs) have shown therapeutic effects over short treatment periods, their long-term use (> 3 weeks) is prohibited due to their adverse effects (Ference and Last 2009). TGCs also have some limitations owing to their low absorption ratio (De Souza and Strober 2008). Furthermore, there are some reports that TGCs may suppress the hypothalamic-pituitary-adrenal axis when applied topically to the dorsal cervical skin (Behrend and Kemppainen 1997). Therefore, many studies have been conducted on alternative drugs. Recently, stem cell therapy has been reported to attenuate cAD (de Oliveira Ramos et al. 2020). Villatoro et al. (2018) demonstrated attenuation of cAD by transplantation of canine adipose-derived mesenchymal stem cells. Villatoro et al. (2018) reported pruritus relief 1 week after treatment, while the other symptoms included in the cAD extent and severity index (CADESI) improved 4 weeks after treatment. No adverse effects were observed up to 6 months after treatment.

In the present study, the pruritus, erythema, pigmentation, dryness, and skin thickness improved after 2 weeks of MFSCE treatment. These results indicated that MFSCE showed a faster therapeutic effect compared to that of conventional stem cell therapy. MFSCE also has the advantage of being non-invasive compared to conventional stem cell therapy. In the present study, we observed no general symptomatic changes to evaluate the adverse effects. In a previous study, we identified that the daily dermal treatment of 0.4 ml of MFSCE for 13 weeks did not have any toxicity in a rodent 13-week repeat-dose toxicity study performed at the Good Laboratory Practice institution (data not shown). The 0.4 ml/head for a rat is converted to 12 ml/head for a dog in using the equivalent dose formula. In the present study, 175 ul of MFSCE (5% of 3.5 ml cream) was administered twice daily for 2 weeks and the anti-AD efficacy was shown. Therefore, we suggest that MFSCE is not toxic, and not expected to show adverse effects in long-term use in dogs.

Although many mechanistic studies have been conducted, the exact mechanism of action of TGC remains unclear. While a previous study identified the anti-inflammatory mechanism of MFSCE in keratinocytes and fibroblasts (Lee et al. 2019), the pathological mechanism of AD remains unclear owing to its complex mechanisms resulting from a combination of various risk factors, including genetic factors, environmental factors, skin permeability, and immune system dysfunction. Chronic inflammation resulting from the overproduction of inflammatory cytokines such as IL-6, IL-5, IL-4, and IL-13 in TH2-polarised $CD4^+$ T cells is an important mechanism of AD (Toshitani et al. 1993). The serum IL-6 concentration is positively correlated with the AD severity (Samochocki et al. 2012). Therefore, IL-6 is an important target for AD treatment. In a previous study, we evaluated the anti-inflammatory effects of MFSCE on tumour necrosis factor-α (TNF-α) and interferon-γ (IFN-γ)-induced inflammatory keratinocytes and fibroblasts in a cell model (Lee et al. 2019). We observed that MFSCE inhibited not only the overexpression of IL-6, but also that of the JAK2/STAT3, NF-κB, and MAPK signalling pathways downstream of the IL-6 signalling pathway. Therefore, these results suggest that MFSCE can attenuate cAD through the suppression of the IL-6 signalling pathway.

In the present study, we evaluated the degree of cAD by measuring the pruritus, erythema as primary lesions and pigmentation, dryness and skin thickness as secondary lesions to the cAD. Therefore, we evaluated all the primary and secondary clinical symptoms. MFSCE significantly decreased the severity of the pruritus, erythema, pigmentation, dryness, and skin thickness. As shown in Figure 3, most of the symptoms of cAD were diminished 14 days

https://doi.org/10.17221/136/2021-VETMED

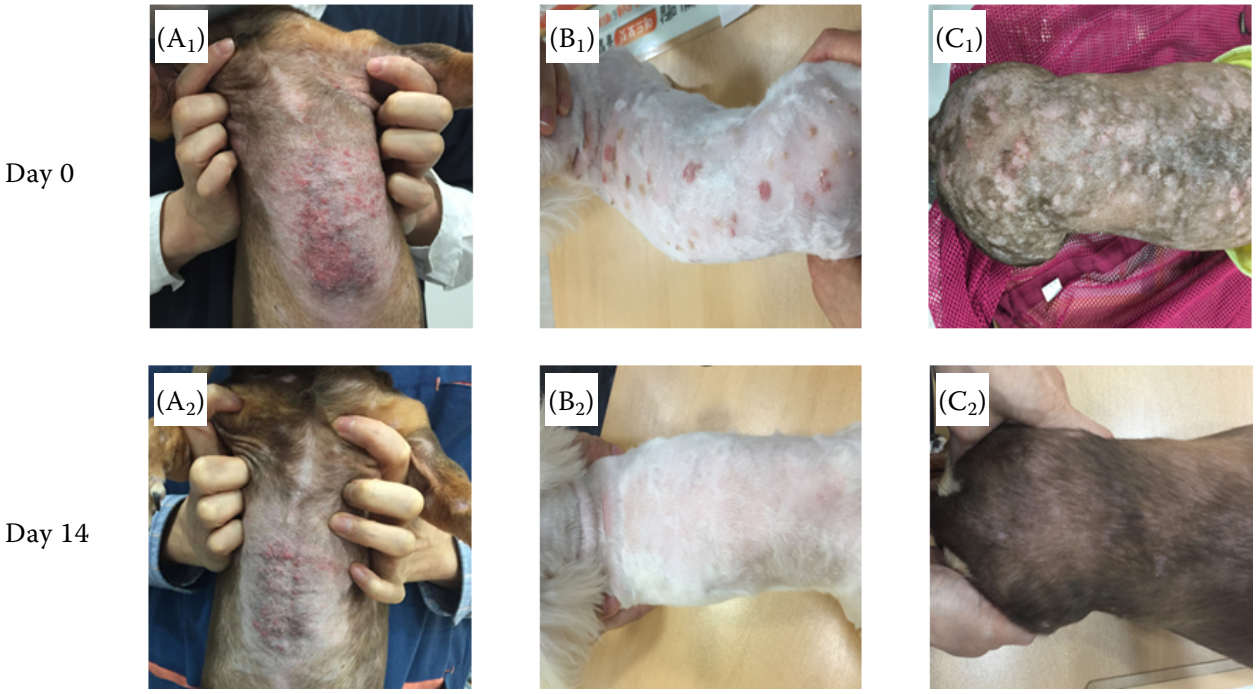

Figure 3. Representative results of the changes in the clinical signs after the membrane-free stem cell extract (MFSCE) treatment

Clinical sign of cAD at day 0 (A_1–C_1) was significantly improved after 14 days of the MFSCE treatment (A_2–C_2)

after MFSCE treatment, compared to day 0. These data indicated that MFSCE attenuated both the primary and secondary symptoms of cAD. Therefore, it is suggested that MFSCE may have potential as an anti-AD agent.

Among the various proteins included in MFSCE, ITGB1 and ANXA1 seem to have main roles of anti-inflammation and wound healing. The anti-inflammatory effect of ITGB1 was identified using LPS-stimulated macrophages (Kong et al. 2020). The anti-inflammatory and wound healing effects of ANXA1 were also identified in various previous studies (Purvis et al. 2019). Therefore, it is suggested that ITGB1 and ANXA1 are the main components of MFSCE for the treatment on atopic dermatitis.

In this randomised, blind, placebo control study, 14 days of treatment with MFSCE improved the clinical signs of cAD with no significant adverse effects. We also found that MFSCE showed excellent therapeutic efficacy over the short-term treatment. In addition, previous studies have confirmed the mechanism of action of MFSCE on cAD and its non-toxicity after long-term administration in rodents (Ha et al. 2022). MFSCE may be a potential treatment option for cAD, but further studies are warranted.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

Behrend EN, Kemppainen RJ. Glucocorticoid therapy. Pharmacology, indications, and complications. Vet Clin North Am Small Anim Pract. 1997 Mar;27(2):187-213.

Cosgrove SB, Wren JA, Cleaver DM, Walsh KF, Follis SI, King VI, Tena JK, Stegemann MR. A blinded, randomized, placebo-controlled trial of the efficacy and safety of the Janus kinase inhibitor oclacitinib (Apoquel®) in client-owned dogs with atopic dermatitis. Vet Dermatol. 2013 Dec;24(6):587-97.

Daltro SRT, Meira CS, Santos IP, Ribeiro Dos Santos R, Soares MBP. Mesenchymal stem cells and atopic dermatitis: A review. Front Cell Dev Biol. 2020 May 14;8:326.

de Oliveira Ramos F, Malard PF, Brunel HDSS, Paludo GR, de Castro MB, da Silva PHS, da Cunha Barreto-Vianna AR. Canine atopic dermatitis attenuated by mesenchymal stem cells. J Adv Vet Anim Res. 2020 Sep 1;7(3): 554-65.

De Souza A, Strober BE. Principles of topical therapy. In: Fitzpatrick TB, Wolff K, editors. Fitzpatrick's dermatol-

https://doi.org/10.17221/136/2021-VETMED

ogy in general medicine. 6th ed. New York: McGraw-Hill; 2008. p. 2643-51.

El Hachem M, Di Mauro G, Rotunno R, Giancristoforo S, De Ranieri C, Carlevaris CM, Verga MC, Dello Iacono I. Pruritus in pediatric patients with atopic dermatitis: A multidisciplinary approach – Summary document from an Italian expert group. Ital J Pediatr. 2020 Jan 30; 46(1):11.

Ference JD, Last AR. Choosing topical corticosteroids. Am Fam Physician. 2009 Jan 15;79(2):135-40.

Forsythe P, Paterson S. Ciclosporin 10 years on: Indications and efficacy. Vet Rec. 2014 Mar;174(Suppl_2):13-21.

Gonzales AJ, Bowman JW, Fici GJ, Zhang M, Mann DW, Mitton-Fry M. Oclacitinib (APOQUEL®) is a novel Janus kinase inhibitor with activity against cytokines involved in allergy. J Vet Pharmacol Ther. 2014 Aug;37(4):317-24.

Ha SE, Vetrivel P, Kim SM, Bhosale PB, Kim HH, Pak JE, Heo JD, Kim YS, Kim GS. Inhibitory effect of membrane-free stem cell components derived from adipose tissues on skin inflammation in keratinocytes. Mol Med Rep. 2022 Apr;25(4):125.

Hillier A, Lloyd DH, Weese JS, Blondeau JM, Boothe D, Breitschwerdt E, Guardabassi L, Papich MG, Rankin S, Turnidge JD, Sykes JE. Guidelines for the diagnosis and antimicrobial therapy of canine superficial bacterial folliculitis (Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases). Vet Dermatol. 2014 Jun;25(3):163-e43.

Jee MK, Im YB, Choi JI, Kang SK. Compensation of cATSCs-derived TGFβ1 and IL10 expressions was effectively modulated atopic dermatitis. Cell Death Dis. 2013 Feb 14; 4(2):e497.

Kern S, Eichler H, Stoeve J, Kluter H, Bieback K. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. Stem Cells. 2006 May;24(5):1294-301.

Kim HJ, Park JS. Usage of human mesenchymal stem cells in cell-based therapy: Advantages and disadvantages. Dev Reprod. 2017 Mar;21(1):1-10.

Kong JS, Park JH, Yoo SA, Kim KM, Bae YJ, Park YJ, Cho CS, Hwang D, Kim WU. Dynamic transcriptome analysis unveils key proresolving factors of chronic inflammatory arthritis. J Clin Invest. 2020 Aug 3;130(8):3974-86.

Lee HJ, Jung M, Kim JH, Yoon NY, Choi EH. The effect of adipose-derived stem cell-cultured media on oxazolone treated atopic dermatitis-like murine model. Ann Dermatol. 2012 May;24(2):181-8.

Lee HJ, Lee SM, Moon YG, Jung YS, Lee JH, Venkatarame Gowda Saralamma V, Kim YS, Pak JE, Lee HJ, Kim GS, Heo JD. Membrane-free stem cell components inhibit interleukin-1α-stimulated inflammation and cartilage degradation in vitro and in vivo: A rat model of osteoarthritis. Int J Mol Sci. 2019 Sep 30;20(19):4869.

Lu L, Dai C, Zhang Z, Du H, Li S, Ye P, Fu Q, Zhang L, Wu X, Dong Y, Song Y, Zhao D, Pang Y, Bao C. Treatment of knee osteoarthritis with intra-articular injection of autologous adipose-derived mesenchymal progenitor cells: A prospective, randomized, double-blind, active-controlled, phase IIb clinical trial. Stem Cell Res Ther. 2019 May 21; 10(1):143.

Marks PW, Witten CM, Califf RM. Clarifying stem-cell therapy's benefits and risks. N Engl J Med. 2017 Mar 16; 376(11):1007-9.

Marsella R. Atopic dermatitis in domestic animals: What our current understanding is and how this applies to clinical practice. Vet Sci. 2021 Jul 2;8(7):124.

Nuttall T. Topical therapy in canine atopic dermatitis: New products. Companion Anim. 2020 Mar;25(2):76-82.

Olivry T, Saridomichelakis M, Nuttall T, Bensignor E, Griffin CE, Hill PB; International Committe on Allergic Diseases of Animals (ICADA). 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. 2014 Apr;25(2): 77-85.

Park HS, Pang QQ, Kim YS, Kim JH, Cho EJ. Neuroprotective effect of membrane-free stem cell extract against amyloid beta 25-35-induced neurotoxicity in SH-SY5Y cells. Appl Sci. 2021;11(5): [12].

Purvis GSD, Solito E, Thiemermann C. Annexin-A1: Therapeutic potential in microvascular disease. Front Immunol. 2019 Apr 30;10:938.

Samochocki Z, Alifier M, Bodera P, Jeziorkowska R, Rosiak E, Jurkiewicz B, Glinska O, Glinski W, Stankiewicz W. T-regulatory cells in severe atopic dermatitis: Alterations related to cytokines and other lymphocyte subpopulations. Arch Dermatol Res. 2012 Dec;304(10):795-801.

Santoro D. Therapies in canine atopic dermatitis: An update. Vet Clin North Am Small Anim Pract. 2019 Jan; 49(1):9-26.

Venkatarame Gowda Saralamma V, Vetrivel P, Kim SM, Ha SE, Lee HJ, Lee SJ, Kim YS, Pak JE, Lee HJ, Heo JD, Kim GS. Proteome profiling of membrane-free stem cell components by nano-ls/ms analysis and its anti-inflammatory activity. Evid Based Complement Alternat Med. 2019 Nov 4;2019:4683272.

Toshitani A, Ansel JC, Chan SC, Li SH, Hanifin JM. Increased interleukin 6 production by T-cells derived from patients with atopic dermatitis. J Invest Dermatol. 1993 Mar;100(3):299-304.

Villatoro AJ, Hermida-Prieto M, Fernandez V, Farinas F, Alcoholado C, Rodriguez-Garcia MI, Marinas-Pardo L,

https://doi.org/10.17221/136/2021-VETMED

Becerra J. Allogeneic adipose-derived mesenchymal stem cell therapy in dogs with refractory atopic dermatitis: Clinical efficacy and safety. Vet Rec. 2018 Dec 1;183 (21):654.

Wu S, Pang Y, He Y, Zhang X, Peng L, Guo J, Zeng J. A comprehensive review of natural products against atopic dermatitis: Flavonoids, alkaloids, terpenes, glycosides and other compounds. Biomed Pharmacother. 2021 Aug;140: 111741.

Received: October 24, 2021
Accepted: April 28, 2022
Published online: June 20, 2022