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LETTER TO THE EDITOR

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Letter regarding "Successful nutritional control of scratching and clinical signs associated with adverse food reaction: A randomized controlled COSCAD'18 adherent clinical trial in dogs in the United States" and "Successful nutritional control of scratching and clinical signs associated with adverse food reaction: A randomized controlled COSCAD'18 adherent clinical trial in dogs in the United Kingdom"

About misappropriating the COSCAD'18 for an unintended use

Dear Editors,

In 2018, the International Committee for Allergic Diseases of Animals (ICADA) published one of the first core outcome sets (COS) in veterinary medicine.[1] The COSCAD'18 includes a minimum set of outcome measures to be used in clinical trials enrolling dogs with atopic dermatitis (AD), thus permitting future meaningful comparisons among different therapeutic interventions and creating the possibility of combining results of different studies in meta-analyses.[1]

It was with great interest that we saw, in a recent issue of the *Journal of Veterinary Internal Medicine*, two articles by Weemhoff et al, whose title stated that the clinical trials were "COSCAD'18 adherent."[2,3]

After reading these articles, it became clear, however, that the COSCAD'18 had been misinterpreted, misappropriated, misused, and misrepresented. We believe that there are some important differences between the intended use of the COSCAD'18,[1] and that reported in these two articles.[2,3]

In the paragraphs below, we will highlight some of these critical differences.

STUDY DESIGN

First, as stated in our international consensus article, "…this COSCAD'18 should be proposed for all therapeutic—but not preventive, prophylactic or proactive—clinical trials enrolling dogs with chronic, nonseasonal (or perennial), moderate-to-severe AD."[1] In contrast, Weemhoff and colleagues recruited dogs that "…had a history of GI signs (tenesmus, diarrhea, or soft feces) with or without dermatological signs (erythema, scratching) related to an adverse reaction to food …currently stable for these clinical signs."[2,3] It is well established that only a fraction of dogs with adverse food reactions (AFRs) manifests them as AD,[4] but it is unclear how many of the dogs enrolled in the Weemhoff trials, if any, had AD.

Second, and as mentioned above, the COSCAD'18 was designed for prospective therapeutic trials.[1] In contrast, Weemhoff et al published the results of two identical studies (one in the United States, one in the United Kingdom) in which two diets were compared for their ability to prevent the recurrence of clinical signs of cutaneous AFRs.[2,3]

Third, in our paper,[1] we specified that the COSCAD'18 would be "most relevant and representative of the true intervention's efficacy in trials lasting 6 weeks or longer." This proposed duration was selected because some of the skin lesions scored with the Canine Atopic Dermatitis Lesion Index (CADLI) or the Canine Atopic Dermatitis Extent and Severity Index (CADESI) instruments are not sensitive to change in short-term trials. In contrast, Weemhoff et al only had a 3-week diet-testing phase.[2,3]

In summary, we had proposed the COSCAD'18 for therapeutic trials lasting 6 weeks or longer and enrolling dogs with moderate-to-severe AD.[1] In contrast, Weemhoff et al used it for two 3-week relapse-prevention trials enrolling dogs with controlled AFRs[2,3]; such a study design is not what had been intended by the ICADA for this COS.

OUTCOME MEASURES

In the COSCAD'18,[1] we proposed the use of a minimum set of three outcome measures summarized below:

1. CADESI4/CADLI normal-to-mild: this corresponds to the percentage of dogs with veterinarian-assessed skin lesions scores in the range of normal dogs or dogs with mild AD at study end (ie, CADESI-4 < 35 or CADLI < 8),
2. Pruritus visual analog scale (PVAS)10 normal-to-mild: this corresponds to the percentage of dogs with owner-assessed pruritus scores in the range of normal dogs or dogs with mild AD at study end (ie, PVAS10 < 3.6), and
3. Owner global assessment of treatment efficacy (OGATE) good-to-excellent: this is the percentage of dogs whose owner rated the overall response to treatment as "good" or "excellent" at study end (ie, OGATE > 2).

In the data collection section of both articles, Weemhoff et al stated that CADLI scores lower than 8 and PVAS scores lower than 3.6 "… were considered clinically normal," and they referenced our COSCAD'18 publication to support this assertion; it was, however, incorrect.

First of all, the CADLI was designed solely for dogs with AD but not for those with other skin diseases, as only typically affected skin areas of AD are to be scored with this instrument.[5] Consequently, this scale was not appropriate for Weemhoff et al to use for dogs with other skin diseases, including non-AD cutaneous AFRs.

Second, Weemhoff et al misinterpreted and misrepresented the assessment of both instruments, as the benchmarks used in their studies did not correspond to those of normal dogs but to those of dogs with normal-to-mild AD/pruritus instead.[1] Indeed, figure 1 of these two articles reveals that, while it seems that the mean CADLI values correspond to scores of normal dogs, those of the PVAS10 do not.[6] When extrapolating the upper range of the 95% confidence interval of the PVAS10 using the mean + 2SD, it is evident that, at both baselines (ie, day 21) and studies' ends (ie, day 42), some dogs had PVAS10 that reflected a moderate, severe, or even very severe pruritus.[6] It is thus unclear how these dogs could be "… currently stable for these clinical signs," as stated by Weemhoff and colleagues.[2,3]

DATA REPORTING

The COSCAD'18 had recommended that the data be reported in a specific manner, including in-paper tables, figures, and a comprehensive online supplementary table with all individual patient data; specific examples were added in the publication's supplementary information.[1] Regrettably, the two papers by Weemhoff et al did not follow any of these recommendations.

CONCLUSION

To conclude, while we applaud the intention of Weemhoff and colleagues to adopt the COSCAD'18, we regret that the first publications that purported to be "COSCAD'18-adherent" disregarded all recommendations made for this COS, especially those regarding study design, patient selection criteria, use of standard outcome measures, and data reporting.

We hope that, in the future, investigators will more closely follow the COSCAD'18 as it was intended, thus permitting meaningful comparisons of therapeutic trials enrolling dogs with AD.

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