Fuzapladib in a randomized controlled multicenter masked study in dogs with presumptive acute onset pancreatitis

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LETTER TO THE EDITOR

Letter regarding "Fuzapladib in a randomized controlled multicenter masked study in dogs with presumptive acute onset pancreatitis"

Dear Editor,

We read with interest the article by Steiner et al,[1] that claims that administration of fuzapladib is safe and effective in reducing 2 clinical scores in dogs with acute pancreatitis (AP). We commend Steiner et al for their efforts in addressing a critical need in veterinary medicine. This letter, however, raises significant concerns regarding the methodology and interpretation of the study results.

1 | ISSUES REGARDING THE STUDY POPULATION AND INCLUSION CRITERIA

Because of its ability to inhibit neutrophil recruitment, fuzapladib may be useful in treating severe cases of AP. However, the study did not include such cases, which was an oversight given that expensive treatments such as fuzapladib are typically reserved for severe cases, especially those that progress to systemic inflammatory response syndrome. Another limitation is the lack of data on the proportion of dogs treated as outpatients (presenting with milder clinical signs and requiring less care) compared with those requiring intensive care. Because IV fluid administration is the cornerstone of AP treatment, detailed information on the number of dogs receiving fluids (including volume and duration) in each group should be disclosed to assess the efficacy of fuzapladib for variable severities of AP. Another issue is the non-mandatory requirement of abdominal pain for inclusion. Overall, the inclusion criteria were lenient because 2 or more clinical signs were deemed sufficient for inclusion. Previous literature has shown that up to 40% of dogs with acute abdomen may have false positive increases of cPLI.[2] While we appreciate that a subset of dogs with AP may initially present with an ultrasonographically normal pancreas, the inclusion of an ultrasonographic diagnosis of AP would have clearly strengthened the study. Some dogs may have only exhibited mild or moderate acute gastrointestinal signs that would likely resolve with minimal care. Additionally, the decision to include dogs with pre-existing medical conditions (with no information on the nature, management, and distribution of these conditions across groups) is another concern that could have influenced treatment outcomes and impacts the validity of the study.

2 | ISSUES REGARDING RANDOMIZATION AND INTENTION-TO-TREAT (ITT) ANALYSIS

We acknowledge that the overall percentage of adverse events (AEs) was similar between treatments. However, upon closer examination of tab. 2, there was an increase in nearly every category of AEs in the fuzapladib group, including more severe AEs. Three dogs showed signs of cardiac arrest, hyperthermia, pruritus/urticaria, cerebral edema, anaphylaxis, and hypertension. None of these AEs occurred in the placebo group. Additionally, 4 dogs died after receiving fuzapladib, and the rate of severe AEs (5%) was higher than expected for a "safe" treatment. If fuzapladib is responsible for the increase in AEs, this warrants a re-evaluation of the drug's benefit/risk ratio. Dogs with severe AP often present with other complications, including bacterial infections. The potential for fuzapladib to compromise the body's response to such infections requires further investigation.

However, if the increase in AEs is independent of treatment, it suggests that the dogs in the fuzapladib group were in worse overall condition at the beginning of the study. This hypothesis is supported by their higher modified clinical activity index (MCAI) scores and the greater number of dogs in this group that did not complete the study. Importantly, this also suggests that randomization was not successful in producing comparable/balanced groups at baseline, which is plausible given the low sample size and large number of investigation sites. In this case, results from the safety and efficacy analyses may be confounded by baseline differences in study groups and are not entirely reliable.

The Methods section states that animals were required to have a cPLI >400 μg/L for inclusion. However, upon closer examination of fig. 1, this requirement was only applied to the efficacy population. Dogs with concentrations below 400 μg/L were also included in the safety evaluation, violating the inclusion criteria (the safety assessment is no longer an ITT analysis). Including dogs with cPLI ≤400 μg/L

may lead to overly optimistic results, compared to an analysis including only dogs that met the inclusion criteria.

3 | ISSUES REGARDING RANDOMIZATION AND PP ANALYSIS

The reasoning behind selecting MCAI as the primary efficacy endpoint (or conducting a further modification of the MCAI post hoc) is unclear. The authors mention that the number of animals per group was based on "the effect size reported in several unpublished studies," but the primary endpoint is not explicitly stated. To interpret statistical values accurately, the primary outcome and statistical analysis must be prespecified. Failure to do so increases the risk of finding false statistical "significance" due to "researchers' degrees of freedom."[3,4] Because the MCAI has only been published in 1 small study of 13 dogs with AP,[5] it seems premature to use it as primary endpoint to assess the efficacy of a drug candidate. Notably, the more established scoring system for AP canine acute pancreatitis clinical severity index (CAPSI)[6] was not included as outcome measure in this study.

To conduct statistical analyses with the primary outcome being the change score, the dependent variable must satisfy several requirements, including having a linear relationship between the post-treatment and the baseline value, avoiding floor/ceiling effects, and having a "smooth" distribution.[7] It is unlikely that several of these conditions were met in this study. Therefore, it would be more appropriate to use the untransformed MCAI score after treatment and adjust the results for baseline as a covariate.[8] The authors state that they have included the MCAI at baseline as a covariate in the model, which may account for these differences and justify the use of change scores. However, the details provided are insufficient for a thorough evaluation of the robustness of the model.

The PP analysis of the efficacy data included 35 dogs across 11 sites. No information is provided about the number of animals per site. With low numbers at each site, the randomization likely did not produce comparable groups at baseline. Site-specific differences, such as the overall quality of care, may affect treatment outcomes in an uneven manner, potentially biasing the results. The noticeable difference in baseline MCAI and total AEs suggests that there may have been an imbalance between groups. Although the site was part of the main repeated measures analysis of covariates (RMANCOVA), the details provided are insufficient to determine if this adequately accounted for potential imbalances between study groups.

Figure 2 shows that the main change in MCAI occurred between D0 and D1. Only 1 dose of fuzapladib had been administered at this point. On D1-3, the decrease in MCAI is essentially the same in both groups. This pattern appears to be more consistent with an initial imbalance in MCAI, with the fuzapladib group potentially starting with poorer health. This, combined with reversion to the mean/baseline effects, likely contributes to the differences between fuzapladib and control, independent of any treatment effect. Whether these differences stem from issues with randomization or not, the distributions of both MCAI values and changes in MCAI between the 2 groups are wide and overlapping. This raises questions about the clinical relevance of these findings, especially because MCAI had not been validated as a surrogate marker of efficacy for AP.

4 | CONCLUSION

Although we do not dismiss the potential of fuzapladib in treating dogs with AP, the lack of sufficient details on the randomization procedure and methodological concerns warrant cautious interpretation of Steiner et al's results.[1] Currently, asserting that fuzapladib has a significant and beneficial clinical impact on this patient population seems premature.

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