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Professor Dennis A Bloomfield
Professor Sandro Vento
Editors-in-Chief, *World Journal of Clinical Cases*

Dear Professors and Editors,

Thank you very much indeed for your e-mail message dated September 16, 2019 concerning our original manuscript by Georgiadou et al entitled **"Efficient management of secondary haemophagocytic lymphohistiocytosis with intravenous steroids and γ-immunoglobulin infusions"** your manuscript ID No: 49599 that is kindly been recommended for minor revision in the *World Journal of Clinical Cases*.

Today we submit our revised manuscript with all changes precisely indicated in the text. Also, I have uploaded an unmarked clean version of the revised manuscript.

We are very grateful to you and the assessor for the helpful and thoughtful recommendations and for your willingness to consider a revised manuscript. We believe that we addressed most of them satisfactorily. All of us feel that our paper has now been significantly improved.

Our point-by-point responses, to the reviewer's comments/suggestions, are as follows (with respect to the marked revised version of the manuscript):

Reviewer:

1. "In the abstract, it is stated that underlying infections were diagnosed in 74%. Please add in the unidentified and mycobacterial categories to ensure that numbers add up".

Reply: Thank you very much for your comment. We agree that we should have been more explicit in the abstract regarding infectious etiology. Therefore, according to your suggestions the precise number of each aetiologic infectious agent has now been clearly indicated in the abstract but also in the text (please see the results section of the abstract and results section, p. 9 of main text).

2. "Were NK cells or sol CD25 measured? If so, please add data to Table 1. If not, please state this".

Reply: We have followed your recommendation and we have now clearly stated that in every-day clinical practice in our hospital, soluble CD25 and NK cell activity cannot be determined as it is

also the case in many other institutes (Please see ref. 6-10). Thus, our clinical decision for sHLH diagnosis had to be based on the rest 6/8 HLH-2004 criteria (Please see Discussion section, p.13, lines 1-4).

3. "The role of IVIG requires further discussion given that this product is always in short supply. Gilardin et al CMAJ. 2015 Mar 3; 187(4): 257–264 cite only grade 3 evidence in support of this intervention. Please succinctly summarise the evidence in support of the use of IVIG in this condition. The section on putative mechanisms of action of IVIG could be shortened".

Reply: We understand the concerns raised by the reviewer. However, there are several investigators –including us (ref. 24,41)- who questioned whether it is rationale all these patients with sHLH, and particularly those with infections- or sepsis-associated haemophagocytosis, to receive intense immunosuppressive treatment (ref. 33,42,44,49-51). Indeed, it has been shown in a number of studies -mainly in children and adulthood- that IVIG is an efficient and safe initial regimen for the treatment of sHLH avoiding in parallel all the adverse events of intense immunosuppressive and cytotoxic treatment (please see our additions and modifications on p.17). A few new references to the already cited have also been added to further strengthen our results (Please see new ref. 53-57). However, in order to satisfy you further, we have also stated now the recent review by Gilardin et al (now new ref. No. 52) in the text indicating that the grade of evidence in support of this intervention is moderate (degree of evidence 3; please see p.17). In addition, the section on the mechanisms of action of IVIG was also shortened according to your suggestions (please see deletions on p.15 and 16).

4. "Please provide outcome data for the 4 patients treated with corticosteroids alone. Why did these patients not receive IVIG?"

Reply: Following your recommendation we have now provided the outcome data on the 4 patients who treated with corticosteroids alone. Actually, these 4 patients were treated with corticosteroids only because IVIG was in short supply at those times in our hospital (Please see Discussion section, p.17).

5. "Please clarify that all four patients with VL who received LAMB achieved complete remission (not quite fully explicit as it reads currently)".

Reply: We have followed your suggestion and we have now clarified that all four patients with VL who received LAMB only achieved complete remission (Please see Discussion section, p.16, lines 8-11).

6. "IVIG commonly induces infusion reactions when administered in the face of active infection. Please add information on tolerability of infusions".

Reply: Following your recommendation we have now added information on tolerability of IVIG infusions. Actually, IVIG administration was well-tolerated by most of our patients. Only three patients reported dyspnea and hypertension which were treated by temporary discontinuation of the infusion and symptomatic therapy (Please see Results section, p.10).

7. "Please carefully proofread the re-submission as there are a number of grammatical and typographical errors".

Reply: We have carefully proofread the re-submitted article and tried to edit all grammatical and typographical errors (please see our extended corrections throughout the text).

This work has not been published nor is under consideration elsewhere and I clearly state that all co-authors have seen and agreed with the contents of the manuscript. In addition, all authors have substantially contributed to this work and they have not any financial, consultant or institutional conflict of interest.

Once again, I would like to thank you and the referee for your helpful suggestions and for giving us the opportunity to submit a revised manuscript. I do hope now that our revised manuscript will be found suitable for publication in the *World Journal of Clinical Cases*.

Best wishes
Sincerely yours,

George N. Dalekos, MD, PhD
Professor of Medicine
Head, Department of Medicine and
Research Lab of Internal Medicine