LETTER TO THE EDITOR

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We appreciate the comments from Drs. Yan, Wang, and Jiang on our publication "Current clinical evidence is insufficient to support HMME-PDT as the first choice of treatment for young children with port wine birthmarks" [1]. We are aware of the recent FDA approval of HMME-PDT as an Investigational New Drug in the United States. We respond to the comments from our Chinese colleagues and further elaborate on the conclusions and concerns as follows.

The statement "... (HMME–PDT) has emerged as the first choice for port wine birthmarks (PWB) treatment, particularly for young children..." was not drawn from the meta-analysis. We provided an observational description of current trends developing in many hospitals in China, despite not yet being reported in the literature. The driving forces underlying such trends are multifactorial, including observed efficacy and nonscientific contributors from treatment tradition, policy, social economics, and marketing. We agree that the "off-label" of an approved drug could be a compliant implementation for HMME use in some pediatric patients (< 14 years old) after its official approval in 2016. However, the compliance for pediatric use before 2016 remains to be clarified, particularly for the studies without a clear statement of Ethics Committee approval or exemption [2, 3].

Both Letters state that "... Phase IV studies of pediatric populations are being undertaken." We agree that Phase IV studies emphasizing pediatric populations are needed. However, it is equally important to provide long-term follow-up data on those pediatric cohorts (> 3000 reported patients and unreported cohorts) who have already been treated with HMME-PDT over several decades in China [3–6]. Except for an early study reporting that no recurrence was observed in patients followed up for longer than 19 years [4], long-term follow-up data is largely absent. What were the overall long-term efficacies in those pediatric patients previously treated by HMME-PDT? Reoccurrence and re-darkening of PWB lesions years after PDL have been reported [7–10]. Was there reoccurrence and re-darkening in any pediatric patients years after HMME-PDT? We look forward to seeing long-term follow-ups from our Chinese colleagues in the future.

Both Letters do not fully address the safety concerns in pediatric patients raised in our publication. Were there any adverse cardiovascular and neurological sequelae in those cohorts compared to their counterparts? We strongly suggest that a complete and systemic set of in vitro and in vivo safety data should be provided before a clinical trial on pediatric patients begins: (1) potential long-term toxicity to normal endothelial cells (ECs), particularly infantile ECs, upon HMME acute exposure; (2) potential adverse effects during pregnancy and fetal development upon HMME exposure; (3) potential penetration of HMME through the blood-brain barrier (BBB) in children; (4) potential neurological effects in children if HMME penetrates through an immature BBB and off-target radiation; and (5) comprehensive pharmacokinetic data in children, including drug clearance, elimination half-life, elimination rate constant, the fraction of the drug excreted in urine, etc.

We strongly urge our Chinese colleagues, laser scientists, and physicians to be extra cautious and consider additional safety evaluations before using HMME-PDT on pediatric patients. Our original conclusion reflects the available data to date and raises potential concerns about this emerging trend.

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Conflicts of Interest

The authors declare no conflicts of interest.

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References

1. C. Gao, V. Nguyen, M. L. Hochman, et al., "Current Clinical Evidence is Insufficient to Support HMME-PDT as the First Choice of Treatment for Young Children With Port Wine Birthmarks," *Lasers in Surgery and Medicine* 56 (2024): 321–333.

2. Y. Zhang, X. Zou, H. Chen, Y. Yang, H. Lin, and X. Guo, "Clinical Study on Clinical Operation and Post-Treatment Reactions of HMME-PDT in Treatment of PWS," *Photodiagnosis and Photodynamic Therapy* 20 (2017): 253–256.

3. K. H. Yuan, Q. Li, W. L. Yu, D. Zeng, C. Zhang, and Z. Huang, "Comparison of Photodynamic Therapy and Pulsed Dye Laser in Patients With Port Wine Stain Birthmarks: A Retrospective Analysis," *Photodiagnosis and Photodynamic Therapy* 5 (2008): 50–57.

4. Y. Gu, N. Y. Huang, J. Liang, Y. M. Pan, and F. G. Liu, "Analyse clinique de 1 949 angiomes plans traités par thérapie photodynamique vasculaire (Gu's PDT)," *Annales de Dermatologie et de Vénéréologie* 134 (2007): 241–244.

5. G. Li-Qiang, W. Hua, N. Si-Li, and T. Chun-Hua, "A Clinical Study of HMME-PDT Therapy in Chinese Pediatric Patients With Port-Wine Stain," *Photodiagnosis and Photodynamic Therapy* 23 (2018): 102–105.

6. B. Zhang, T. H. Zhang, Z. Huang, Q. Li, K. H. Yuan, and Z. Q. Hu, "Comparison of Pulsed Dye Laser (PDL) and Photodynamic Therapy (PDT) for Treatment of Facial Port-Wine Stain (PWS) Birthmarks in Pediatric Patients," *Photodiagnosis and Photodynamic Therapy* 11 (2014): 491–497.

7. J. S. Nelson, W. Jia, T. L. Phung, and M. C. Mihm Jr., "Observations on Enhanced Port Wine Stain Blanching Induced by Combined Pulsed Dye Laser and Rapamycin Administration," *Lasers in Surgery and Medicine* 43 (2011): 939–942.

8. J. A. Savas, J. A. Ledon, K. Franca, A. Chacon, and K. Nouri, "Pulsed Dye Laser-Resistant Port-Wine Stains: Mechanisms of Resistance and Implications for Treatment," *British Journal of Dermatology* 168 (2013): 941–953.

9. F. Messele, W. Van Trigt, L. Arkin, C. C. W. Hughes, and K. M. Kelly, "Port Wine Birthmark Therapy: A New Direction," *Lasers in Surgery and Medicine* 56 (2024): 529–531.

10. M. Chou, M. Karim, J. Josephs, T. Itzkowitz, M. R. Dreker, and J. G. Labadie, "Pulsed Dye Laser and Adjuvant Topical Therapies for the Treatment of Port-Wine Stains: A Systematic Review," *Lasers in Surgery and Medicine* 56 (2024): 39–44.