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STEM CELLS TRANSLATIONAL MEDICINE

In Reply

We thank Dr. Finlay-Morreale for comments about our publication entitled "Outcomes of bone marrow mononuclear cell transplantation combined with interventional education for autism spectrum disorder."[1,2] Please rest assured that we appreciate any constructive criticism, and we take any concerns expressed very seriously. We would like to clarify some of the issues stated in the letter.

As we all know, the incidence and prevalence of autism seems to be increasing worldwide.[3] So far, educational intervention is still considered the standard treatment for children with autism, but unfortunately, there are still many children who do not respond well to this method.[4,5] That is why other treatments—including stem cell infusions—are being studied.

With regard to your question concerning the cell transplants, we infused mononuclear cells from bone marrow containing hematopoietic stem cells and progenitor cells. Although mechanisms of action remain to be studied, their ability to secrete bioactive molecules and to migrate rapidly to inflammation sites has attracted great interest in their use for autism.[6-9] In addition, bone marrow mononuclear cells contain precursors of mesenchymal stem/stromal cells, and human muse cells (nontumorigenic pluripotent-like stem cells).[10-12] We specified the number of mononuclear cells, $CD34^+$ hematopoietic stem cells, and progenitor cells in the section "BMMNC transplantation": "The average mononuclear cell and $CD34^+$ cell counts per kg body weight were 42.3×10^6/kg and 2.6×10^6 for the first transplantation and 40.9×10^6/kg and 2.1×10^6 for the second transplantation, respectively."

The second concern expressed in the letter was the safety of intrathecal injection. It is well established that lumbar puncture and intrathecal infusion are standard procedures in modern medicine. This approach has been commonly used for pain relief during or after operations.[13-16] In children, this route is also used in the treatment of cerebral palsy with the administration of Baclofen or in the context of stem cell infusions.[17-22] Reports have shown that this is a safe procedure, without serious complications, and with low incidence of minor accidents. In our study, 26 minor adverse events (AEs) related to the intervention, which occurred during the first week of infusion, included pain, broken vein, peripheral vein masonry, and slipping needle out of the vein during infusions. The 17 AEs including mild fever, nausea, and vomiting occurred during the 18-month follow-up period.

Stem cell infusion through the intrathecal route for autism has been used by some authors before us. Reports have also shown this route to be safe, with low incidence of side effects.[23,24]

We understand that intravenous stem cell transfusion would be less invasive than intrathecal. However, studies have shown that the majority of stem cells could not reach the brain because most have been trapped in the lungs and spleen,[25] a problem often described as first-pass effect, rendering the infusions largely ineffective.

All patients in our study underwent educational intervention before the mononuclear cell infusion with an average duration of 34 ± 17.5 months. However, improvements were marginal and CARS scores still placed them in the "severe" category of autism. Post-infusion monitoring revealed increased progress that was tracked over time, specifically over the course of 18 months in total, exhibiting sustainable results during and throughout that follow-up period.

Limitations in our study, such as no control group, were indeed highlighted in our article, and we also recommended that a future study including a control group is required to accurately conclude the benefit of stem cells in improving autism disorders. Furthermore, we have always believed that even given the potential of stem cell infusions, a combination with educational intervention is still very important to help achieve significant changes in the quality of life of children with autism.

In conclusion, our study demonstrated that repeated bone marrow mononuclear cell infusion via intrathecal route is safe and provides initial evidence for a significant improvement in clinical outcomes for children suffering from autism spectrum disorder, justifying a future randomized, fully controlled clinical trial.

CONFLICT OF INTEREST

M.H. declared an advisory role for Regenerative Medicine at Vinmec International Hospital. The other authors declared no potential conflicts of interest.

Liem Nguyen Thanh[1], Hoang-Phuong Nguyen[1], Minh Duy Ngo[2], Viet Anh Bui[3], Phuong T.M. Dam[3], Hoa Thi Phuong Bui[3], Doan Van Ngo[2], Kien Trung Tran[1], Tung Thi Thanh Dang[2], Binh Duc Duong[2], Phuong Anh Thi Nguyen[2], Nicholas Forstyth[4], Michael Heke[5]

[1]*Vinmec Research Institute of Stem Cell and Gene Technology (VRISG), Hanoi, Vietnam*

[2]*Vinmec Times City International Hospital, Hanoi, Vietnam*

[3]*Vinmec Hightech Center, Vinmec Health Care System, Hanoi, Vietnam*

[4]*Faculty of Medicine & Health Sciences, Keele University, Newcastle, UK*

[5]*Department of Biology, Stanford University, Stanford, California*

ORCID

Liem Nguyen Thanh https://orcid.org/0000-0002-4036-0161

Hoang-Phuong Nguyen https://orcid.org/0000-0001-9544-5835

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