


Author Response: Correlation of L-asp Activity, Anti-L-asp Antibody, Asn and Gln with Adverse Events Especially Anaphylaxis Risks in PEG-asp-Contained Regime Treated Pediatric ALL Patients

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Dear editor,

Thanks for giving me a chance to reply to the letter you received about my paper entitled “Correlation of L-asp activity, anti-L-asp antibody, Asn and Gln with adverse events especially anaphylaxis risks in PEG-asp-contained regime treated pediatric ALL patients”. We really appreciate the opinion and comments on my work.

Inactivation is a major challenge in the treatment of PEG-asp, which leads to clinical allergy and silent inactivation. Early drug monitoring and intervention (eg switching to Erwinia asparaginase) are important ways to prevent useless continuation of an inactive drug, which may lead to a worse outcome.^{1,2} So day 7 was chosen to measure the PK/PD parameters, and correlation of these parameters with risk of AEs especially anaphylaxis was analyzed. Sustainably monitoring of L-asp activity would be decided by physicians according to patients’ individual condition, but not the way reported in this study. In addition, as mentioned in the Discussion Section,³ the sustainably monitoring of L-asp activity, anti-L-asp antibody, Asn and Gln levels at multiple time points is still proceeding now.

The absence of anti-PEG-asp antibody measurement in this study was based on the assumption that there was cross-reactivity between native E. coli-asp and PEG-asp.⁴ It was supposed that immunogenic epitopes were shielded by pegylation and a small part of unpegylated drug during degradation that was responsible for antibody production. However, we agree with the need for further study on antibodies and mechanism of immunogenic response to PEG-asp.

Glutamine depletion is due to the catalysis of asparaginase on hydrolysis of glutamine (Gln) to glutamate (Glu) as well as asparagine (Asn) to aspartate (Asp) in ALL treatment.^{5,6} Furthermore, Gln is required for de novo Asn biosynthesis in mammalian cells, purine and protein biosynthesis in leukemic

cells,^{7,8} leading Gln depletion to be a potential indicator of anti-leukemic effect. Therefore, in addition to Asn level, day 7 post-treatment measurement on the Gln level was conducted to analyze and explore the activity as well as efficacy of PEG-asp from another perspective.

For patients with plasma drug activity <100U/L, Erw-asp was administered at a dose of 20 000 U/m² by intramuscular injection twice a week. Trough L-asp activity levels were monitored, and 6 of 7 patients (85.7%) had at least one trough L-asp activity level >100U/L, while the dose was adjusted for the other one patient. The differences between these data and those reported by Kloos et al.⁹ may be due to the small sample size and differences in route of administration and the race of the subjects.

Ethical Statement

This study was approved by the Ethics Committee of Shanghai Children’s Medical Center, Shanghai Jiao Tong University School of Medicine with an ethical approval number of SCMCIRB-K2017065. All guardians of pediatric patients signed the informed consents before enrollment.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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