

# Native *E. coli* asparaginase upfront should be replaced by PEGasparaginase upfront in the treatment of pediatric patients with acute lymphoblastic leukemia

To the editor,

Pegylated *Escherichia coli* asparaginase (PEGasparaginase) is used more frequently upfront in the treatment of acute lymphoblastic leukemia (ALL).<sup>1-5</sup> Comparison studies between native *Escherichia coli* (*E. coli*) asparaginase upfront versus PEGasparaginase upfront have been conducted.<sup>6-8</sup> For instance, the recent study of the St. Jude Children's Research Hospital is of interest.<sup>9</sup> Liu *et al.* found that PEG, and not L-ASP, is the major antigen that causes allergic reactions.<sup>9</sup> This is an important conclusion as Mesegué *et al.* conducted a meaningful clinical study, and they concluded that PEGasparaginase used upfront was associated with a lower incidence of a clinical allergy to PEGasparaginase.<sup>10</sup> This is consistent with the recent results of Kloos *et al.*<sup>4</sup>

Mesegué *et al.* analyzed one hundred and twenty-six children (not including infants) who were diagnosed with ALL from 2013 to 2020.<sup>10</sup> This study is quite interesting and also a novel one as two different treatment regimens were compared within the same ALL protocol. A new kind of study approach and also a rare one as native *E. coli* asparaginase is not used any more upfront in most European countries and in the US.

To better understand this study, we should go a little back in time. The normal (and usual) PEGasparaginase dosage is 2500 IU/m<sup>2</sup>.<sup>6</sup> The frequently cited study from the Dana-Farber Cancer Institute (DFCI) 91-01 showed that patients who tolerated 25 or fewer weeks of asparaginase had a significantly worse outcome than those who received at least 26 weeks of asparaginase.<sup>6</sup> Dutch researchers conducted in 2014 a prospective study with the same dosage regimen in the intensification phase of children treated for ALL.<sup>11</sup> Tong *et al.* concluded that patients who did not show a clinical allergy to or silent inactivation of PEGasparaginase, the serum levels were too high using a schedule of 2500 IU/m<sup>2</sup> every other week.<sup>11</sup> Based on this finding, the administered PEGasparaginase dose can be lowered to 1500 IU/m<sup>2</sup> which was studied recently.<sup>4</sup> In the study of Mesegué *et al.*, the levels of asparaginase activity were also high using of 1000 IU/m<sup>2</sup> intramuscular (IM).

Remarkably, the peak levels of asparaginase activity in the study of Mesegué *et al.* were in the same range as the trough levels when using 1000 IU/m<sup>2</sup> PEGasparaginase IM.<sup>10</sup> Tong *et al.* found higher peak levels of asparaginase activity as compared to the trough levels.<sup>11</sup> It should be noted that the Dutch researchers used an

intravenous (IV) route of administration. So, the modus of administration seems to influence the asparaginase kinetics, suggesting that IM administration leads to stable asparaginase activity levels. Unfortunately, no in-depth pharmacokinetic (PK) research was conducted in the study of Mesegué *et al.*, so a pharmacological explanation for the stable activity levels administered intramuscularly remains unanswered.

A lower asparaginase dosage could lead to less toxicity,<sup>12</sup> this was already suggested by Tong *et al.* when using PEGasparaginase IV.<sup>13</sup> Mesegué *et al.*<sup>10</sup> performed linear mixed models, this is in general in line with the analysis of Tong *et al.*<sup>13</sup> In the original publication of Mesegué *et al.*, the toxicity data were published and associated with peak levels (7 days after each PEGasparaginase dose) and its trough levels. The following Figure (1A,B, and C) were created in R: A language and environment for statistical computing, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria, [www.R-project.org](http://www.R-project.org)) using the packages: *ggplot2* and *dplyr*. The R lme (linear mixed effects models) function of the nlme (nonlinear mixed effects models) package was used to perform statistical analysis on these data, <https://CRAN.R-project.org/package=nlme>, R package version 3.1-152.

Ammonia (Figure 1A) and triglyceride levels (Figure 1B) were associated with the asparaginase activity levels, however for triglyceride this association was not significant ( $p = 0.084$ ) and significantly different for ammonia ( $p = 0.013$ ).<sup>14</sup> Also, we found a negative association between albumin (Figure 1C) and asparaginase activity levels ( $p < 0.0001$ ), which is in line with a recent report.<sup>15</sup> This could be explained by the fact that asparaginase can alter synthesis of proteins, leading to severe acquired deficiencies.<sup>16</sup> Kloos *et al.* found previously that using therapeutic drug monitoring (TDM) and its effect of the reduced asparaginase activity levels on the toxicity was limited.<sup>4</sup>

To conclude, Mesegué *et al.*<sup>10</sup> found similar results as Tong *et al.*<sup>11,13</sup> The added value of this study is that it shows that there is rationale to switch from native *E. coli* asparaginase to its pegylated form, also in the low-income countries. PEGasparaginase can be administered IV. When using IM, which is the normal usual way of asparaginase administration in Spain, this is associated with more anxiety in the patients.<sup>8</sup> In line with the previous reports using PEGasparaginase upfront in children with newly diagnosed ALL is also supported by the data of Mesegué *et al.*<sup>10</sup>

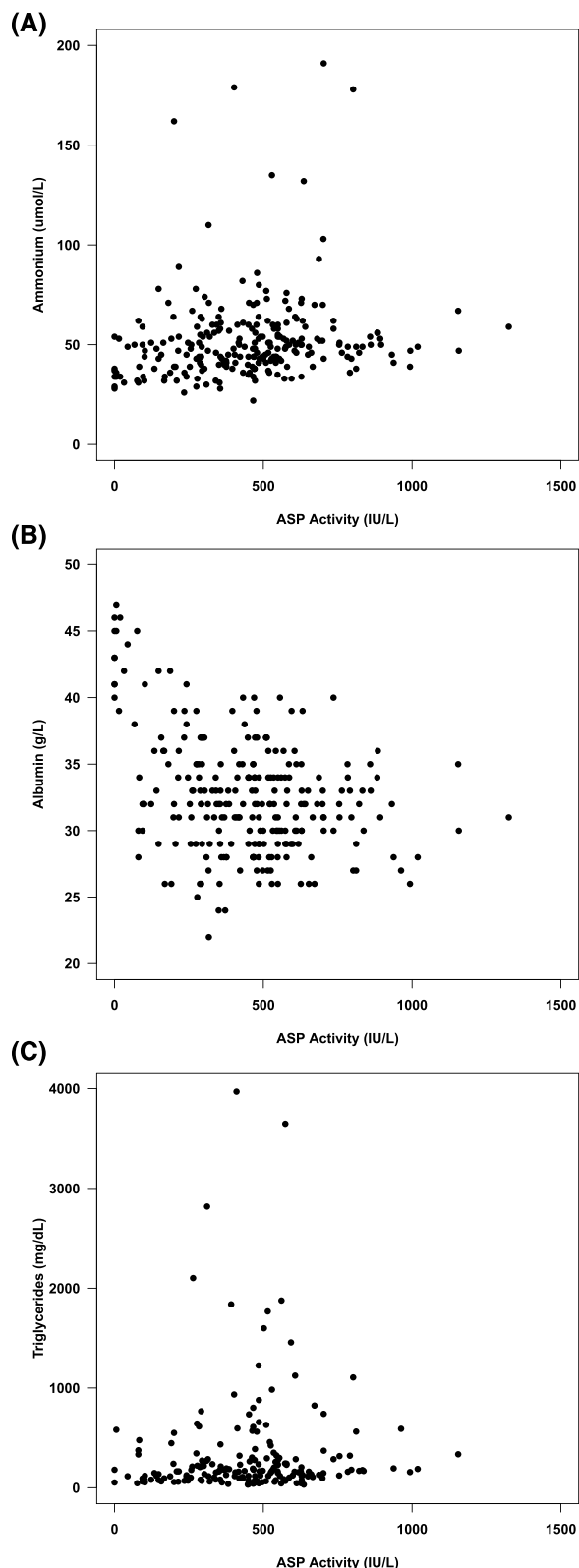


**FIGURE 1** (A) The ammonia levels in children with or without inactivation of pegylated *Escherichia coli* asparaginase (PEGasparaginase) are shown. Please note that on the X-axis the trough PEGasparaginase activity levels are included. R: A language and environment for statistical computing, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria, [www.r-project.org](http://www.r-project.org)). We used the next packages: *ggplot2* and *dplyr* to create

all part figures (A, B, and C). The R lme (linear mixed effects models) function of the nlme (nonlinear mixed effects models) package was used to perform statistical analysis on these data, <https://CRAN.R-project.org/package=nlme>, R package version 3.1-152. Linear mixed models were used to assess the association between asparaginase activity levels and ammonia levels to account for the correlation between the measurements from the same subjects. A two-sided  $p$ -value  $< 0.05$  was considered statistically significant. The level of asparaginase activity of 100 U/L or greater is associated with complete asparagine depletion (lower level of quantification of 0.2  $\mu\text{mol/L}$ ). The summary output is: for every 100 units of asparaginase activity level increase, ammonia increases 1.5 units ( $p = 0.013$ ). The percentage of variation absorbed by the correlation between the subjects can be quantified with the intraclass correlation coefficient (ICC) of this model. This ICC for the model including ammonia is 0.02 (calculated out of 1). (B) The albumin levels in children with or without inactivation of PEGasparaginase are shown. Linear mixed models were used to assess the association between asparaginase activity levels and albumin levels to account for the correlation between the measurements from the same subjects. The summary output is: for every 100 units of asparaginase activity level increase, albumin increases 0.67 units ( $p < 0.0001$ ). This ICC for the model including albumin is 0.21 (calculated out of 1). (C) The triglyceride levels in children with or without inactivation of PEGasparaginase are shown. Linear mixed models were used to assess the association between asparaginase activity levels and triglyceride levels to account for the correlation between the measurements from the same subjects. The summary output is: for every 100 units of asparaginase activity level increase, triglyceride increases 26.9 units ( $p = 0.084$ ). This ICC for the model including triglyceride is 0.60 (calculated out of 1)

## KEYWORDS

albumin, allergy, ammonia, asparaginase activity levels, *Erwinia* asparaginase, pediatric acute lymphoblastic leukemia, PEGasparaginase, pharmacokinetics, triglyceride

## CONFLICT OF INTEREST

Montserrat Mesegué reports speaker fees and travel and accommodation support from Shire/Servier. José Luís Dapena reports advisory board honorarium, speaker fees, and travel and accommodation support from Jazz Pharma and Shire/Servier. Mireia Camós reports speaker fees from Shire/Servier. Susana Rives reports advisory board honorarium, speaker fees, and travel and accommodation support from Jazz Pharma and Shire/Servier. Wing H. Tong, the corresponding author, reports no conflict of interest.

## ETHICS STATEMENT

This letter to the editor did not require an ethical board approval because it did not contain human or animal trials.

## AUTHOR CONTRIBUTIONS

All authors have performed the research and contributed significantly to the paper. Wing H. Tong drafted this letter to the editor and revised it. All authors approved the submitted and final version.

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#### DATA AVAILABILITY STATEMENT

The data that support the findings of this letter to the editor are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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#### PEER REVIEW

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