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Reply to: Pharmacologic Considerations in Antithymocyte Globulin Exposure Calculation

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To the Editor:

We thank Admiraal and colleagues for their detailed and constructive comments on our article. We begin by pointing out that we mentioned most of the limitations that Admiraal et al. describe in the Discussion of our article. In particular, we highlighted the limitations of our estimation of missing values (antithymocyte globulin [ATG] C_{max} and day 14 level) and estimation of ATG clearance.

We agree that calculating an area under the curve (AUC) using a multicompartmental population pharmacokinetic (PK) model is preferable to using trapezoidal method (that we applied). However, to generate a population PK model would require more frequent sampling (we collected only 4 samples per patient in all patients). We are currently collecting 12 samples per patient to generate a population PK model to overcome this limitation in future studies. As correctly pointed out by Admiraal and colleagues, this will also allow us to include patients with incomplete sampling. Nevertheless, it is likely that any over- or underestimation by the trapezoid method is proportional (eg, patient A having a 2-fold higher pre-AUC than patient B using the population PK model will likely have approximately 2-fold higher pre-AUC using the trapezoidal method). Therefore, the main conclusions of our study on the associations of AUCs with factors that influence them and with outcomes are unlikely to change.

As for the overestimation of pre-AUC using the trapezoidal method, in our latest article on the subject we addressed this by using a correction factor for the calculation of the pre-AUC [1]. Nevertheless, we agree that calculating the pre-AUC using a population PK model is even better.

As for the discrepancy between the pre-AUCs shown in our Figure 3A versus those calculated by Admiraal et al., Admiraal et al. are correct. On review of our database, we found a numerical inaccuracy in the formula for pre-AUC that applied to all patients equally and in the same direction. After correcting this error, our median pre-AUC is 288 mg·h/L. This error has been corrected in the final version of the manuscript. Because all pre-AUC values were affected by the error equally, only the absolute pre-AUC values were inaccurate: The analyses of the associations between pre-AUCs and clinical outcomes or factors impacting the pre-AUCs were unaffected. The reason for the median pre-AUC being 288 and not 332 mg·h/L as calculated by Admiraal et al. may be in part because the time value for the first trapezoid (beginning of first ATG infusion to end of last ATG infusion) was a median of 48 hours in our dataset as compared with the 52 hours estimated by Admiraal et al.

As much as we agree with the need of using a population PK model in future studies, this will also have limitations. In the words of British statistician George E. P. Box, "all models are wrong, but some are useful" [2]. Every PK model will have inaccuracies and assumptions, and none will perfectly describe actual biologic exposure. We are particularly concerned about applying a population PK model derived from a certain population/transplant setting (eg, age, conditioning, ATG infusion timing in relation to conditioning chemo/radiotherapy administration and graft infusion, graft type, or graft-versus-host disease prophylaxis other than ATG) to another population/setting. It remains to be determined whether a population PK model for ATG derived in 1 transplant setting/population can be reliably applied to a different transplant setting/population. For that reason we did not use Admiraal et al.'s model [3] to calculate our AUCs, because that model was derived from a setting quite different from ours (eg, nonmyeloablative versus myeloablative conditioning and ATG started on day −8, ie, before severe lymphopenia, versus on day −2, when blood lymphocytes were typically barely detectable). It is conceivable that in the setting of severe lymphopenia factors other than lymphocyte count may play a role in ATG PK, such as IgG level. In addition, it is important to create the population PK model using patients with frequent sampling, including sampling times around the critical time events like graft infusion. Perhaps because the population PK model of Admiraal et al. was not derived from a population in which all or most patients had samples collected immediately before the start and soon

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after the end of the graft infusion, the association between the graft lymphocyte content and post-AUC may have been missed [3].

In summary, we thank Admiraal et al. for their comments. Nevertheless, the problems pointed out by Admiraal et al. are unlikely to influence the major conclusions of the article, notably that high post–hematopoietic cell transplant AUC of ATG capable of binding to lymphocytes is strongly associated with a low risk of acute graft-versus-host disease, that the post-AUC is strongly influenced by graft lymphocyte content and absolute lymphocyte count on the day of starting ATG, and that pre-AUC is strongly influenced by the absolute lymphocyte count.

REFERENCES

1. Dabas R, Jamani K, Kangarloo SB, et al. Anti-relapse effect of pre-transplant exposure to Thymoglobulin. *Blood Advances*. 2019.
2. Box GEP. An Accidental Statistician: The Life and Memories of George E. P. Box. Hoboken, NJ: John Wiley & Sons; 2013.
3. Admiraal R, Nierkens S, de Witte MA, et al. Association between anti-thymocyte globulin exposure and survival outcomes in adult unrelated haemopoietic cell transplantation: a multicentre, retrospective, pharmacodynamic cohort analysis. *Lancet Haematol*. 2017;4:e183–e191.