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Pharmacological Considerations in Antithymocyte Globulin Exposure Calculation

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To the editor:

With much interest, we read the article published by Jamani et al. [1] in *Biology of Blood and Marrow Transplantation*. The authors describe the pharmacokinetics of antithymocyte globulin (ATG) and investigate the relationship between ATG exposure and outcome. Most notable are the findings that low area under the curve (AUC) of ATG before graft infusion led to worse chronic graft-versus-host disease and relapse-free survival, while low AUC after graft infusion was associated with higher risk on acute graft-versus-host disease incidence.

This article is an important addition to the growing body of evidence showing that ATG exposure is an important predictor for clinical outcome. Furthermore, optimal ATG exposure differs may even be different across populations, stem cell sources, and conditioning intensity. We previously reported on the optimal ATG exposure in pediatric patients mainly receiving cord blood and bone marrow after myeloablative conditioning [2,3] and in adult patients following reduced-intensity conditioning for peripheral blood stem cell transplant [4]. The current work helps fill in some gaps of knowledge in a cohort of adults receiving mainly peripheral blood stem cell after myeloablative conditioning.

Still, some major pharmacological limitations to the current article make interpretation of the result difficult. The authors calculate exposures using the trapezoidal method in a rather sparsely sampled set of patients. This method approximates the integral of a curve (such as AUC in a concentration-time curve) and assumes that drug concentrations between samples make a linear decline or increase [5]. The authors used a log-linear trapezoidal rule, in which trapezoids are approximated on a linear scale with increasing concentrations (equation 1), while logarithmic transformation of data is used in decreasing concentrations (equation 2) [5].

$$AUC = \frac{C_i + C_{i+1}}{2} * \Delta t \quad (1)$$

$$AUC = \frac{C_i + C_{i+1}}{\ln\left(\frac{C_i}{C_{i+1}}\right)} * \Delta t \quad (2)$$

In a situation with small time windows between intervals or true linear increase or decrease in concentration, the estimated AUC may be close to true AUC [5], which, however, is not the case in the current study.

To illustrate these inaccuracies, we simulated a typical patient, as described by Jamani et al. [1], receiving the ATG dosing regimen as used in their study (75 kg, day −2 lymphocyte count of 0.1×10^9/L, infusion time 4 hours). A validated population pharmacokinetic model was used to compile a complete concentration-time profile [4] (Figure 1). Although no concentration data are published in the current study, the concentrations seem to be in line with previously published data [6] from the same group using the dose studied in Jamani et al. [1]. With this continuous curve, AUCs were calculated. Visually, the marked overestimation of pre-haematopoietic cell transplantation (HCT) AUC is evident (233 mg*h/L versus 332 mg*h/L in the model based and trapezoidal method, respectively), an overestimation of 49%. Of note, these values are significantly higher than those shown in Figure 3a in Jamani et al. [1]. The authors may have made a miscalculation as, according to equation 1, just the first trapezoid (from 0 mg/L at T = 0 to ~10 mg/L[6] at T = 52 h) has a surface of $\frac{0+10}{2} * 52 = 260$ mg*h/L. For post-HCT AUC, the differences were smaller, while the values for post-HCT AUC that we calculated using logarithmic trapezoids were higher than those calculated by the authors.

On a different subject, the authors try to identify factors that influence ATG AUC (Table 2 in Jamani et al. [1]). Besides the previously reported absolute lymphocyte count (ALC), they suggest that BMI and IgG influence AUC. Obviously, time

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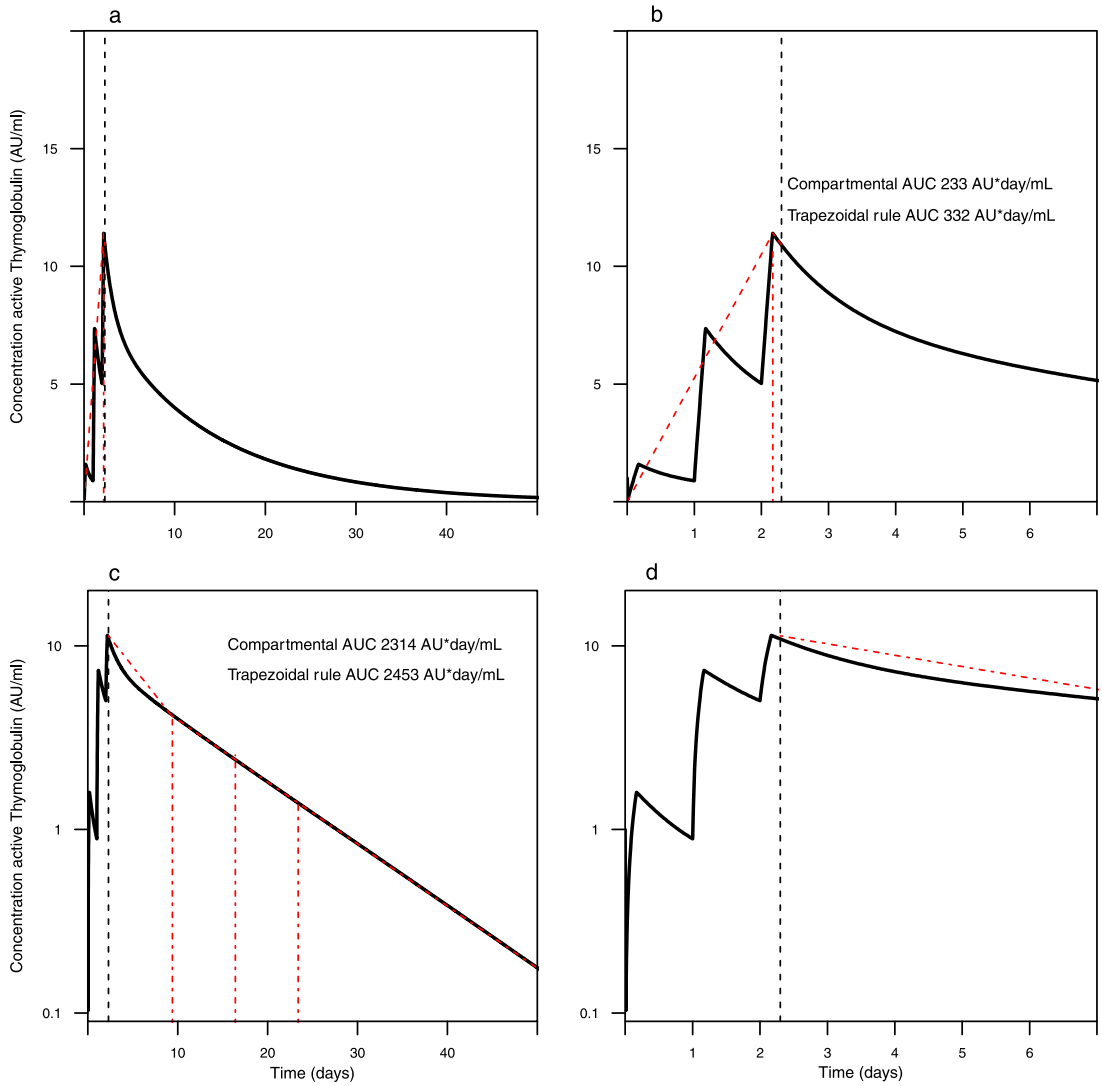

Figure 1. Simulated antithymocyte globulin (ATG) concentration-time curves with a linear Y-axis (a, b) and a logarithmic Y-axis (c, d). Black solid lines: ATG concentrations; black dashed line: infusion of the graft; dashed red lines: trapezoids (note that one vertical line is overlapping with the stem cell infusion).

between last dose of ATG and graft infusion affects pre-HCT AUC, as Δt (equation 2) increases. The association between any weight-based parameter and AUC is no surprise, as AUC is the quotient of dose and clearance. The dose in this study is weight dependent (mg/kg), and thus AUC is weight dependent. The authors also make inferences on predictors of ATG clearance, where clearance is calculated by dividing the total ATG dose by the total AUC. Given the points raised above on AUC estimation, the calculation of clearance may also be biased. The observed association between graft lymphocyte count and IgG is interesting. In our pediatric analyses, both were explored as predictors for pharmacokinetic parameters and found nonsignificant, while in adult analyses, only graft-infused T cell numbers were available and found nonsignificant. Variability however was low, especially for IgG.

Last, quite some concentration data are missing. While washout data (days +7, +14, +28) can easily be extrapolated from other samples, the samples missing at C_{max} and around the graft infusion seem to be more problematic. Given the complex interaction between distribution, clearance, and, as the authors suggest, the influence of graft lymphocytes, it seems virtually impossible to give an exact estimation of these missing concentration data without using mathematical modeling software.

In our opinion, this large, sufficiently sampled, and homogeneously treated population harbors a wealth of information that warrants a robust analysis. However, the limitations stated above, combined with those stated by the authors, themselves make the presented results difficult to interpret. We encourage the authors to perform a population pharmacokinetic analysis, both for robust estimation of pharmacokinetic parameters and AUCs and as an external validation study for our previously reported model. This approach may also prevent the exclusion of around 50% of patients due to some missing samples.

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