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Antithymocyte Globulin: Indiscriminate Use and Complications

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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The safety profile of rATG is impressive, with its use in 40% of inductions in living donor transplants in the US, with a reduced incidence of acute rejection, a low incidence of CMV infections with universal prophylaxis and enabling steroid sparing regimes.

MeSH Keywords: Cytomegalovirus Infections • Graft Rejection • Immunosuppressive Agents • Kidney Transplantation

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Dear Editor,

We read with great interest the paper by Bayraktar et al. in which they concluded that a higher dose of anti-thymocyte globulin (ATG) induction in high-risk patients is associated with an increased risk of cytomegalovirus (CMV) disease and kidney recipient death [1]. We would like to make the following comments.

Their study was designed to evaluate the risk of viral disease in kidney recipients who received induction with either ATG (Fresenius) [fATG] or Basiliximab (BX). It started out as a comparison of the risk of viral infection and recipient death with the use of these 2 induction agents, but concluded that CMV disease was significantly higher in the fATG group compared to recipients who received 'no induction'. This is contrary to their objective, because the 15 patients who received induction with BX were surprisingly excluded from the study.

The 3 study groups were: no induction (low-risk), only fATG (standard-risk), and fATG with BX (high-risk). The high-risk group received a unique and novel combination of fATG and BX, but the rationale for this cocktail is unexplained. Of the 150 patients in the standard-risk and high-risk groups, 147 received deceased donor (DD) kidneys, which have a different risk profile than living donor (LD) kidneys. Data on cold ischemia time and DGF in these patients was not provided, although these are factors that can directly influence the duration and intensity of induction. Recipients in the standard-risk group (101/104) who received fATG had the lowest incidence of acute rejection (AR), yet had the highest incidence of CMV disease, despite valganciclovir prophylaxis. The authors claim that the extended use of fATG with its T-cell depletion is an infection risk, but do not explain what extended use is. We feel it is not the ATG, but its indiscriminate use that is the problem, especially since valganciclovir prophylaxis has been shown to adequately prevent CMV infection in recipients who received ATG [2].

The authors reported that 20% of their kidney recipients developed CMV disease because of the AR episodes and intense immunosuppression, the latter being a natural consequence of treating AR with steroid boluses [3], yet the highest incidence of CMV disease was noted in the group with the lowest ARs. Their conclusion that higher ATG dosage is associated with increased risk of CMV disease and death is not supported by current evidence. The TAILOR study, assessing induction

data (rATG vs. BX) in 2322 living donor kidney recipients from 49 US centers, showed that, with a mean cumulative rATG dose of 5.29 mg/kg, 99.1% were free of infection-related death after 5 years [4]. The AR rates were also significantly lower and milder (BANFF grade 1), with no grade 3, despite its use in higher-risk subgroups such as those receiving kidneys from unrelated donors and re-transplants [4]. Ninety percent of patients in this study received prophylaxis, with a 12-month CMV infection incidence rate of 4.2%, in contrast to a 20% CMV incidence rate in the authors' study, despite all their patients receiving a 3-month valganciclovir prophylaxis. In our opinion, appropriate dosage of rATG is safe and not associated with an increased risk of CMV disease, especially in the era of valganciclovir prophylaxis. The authors used fATG, which has an extremely wide dose range (2–5 mg/kg/day for 5–15 days), and it remains unclear what determined the quantity each recipient received, especially since there is no data provided on delayed graft function (DGF), which usually necessitates an increased requirement of ATG. The recommended cumulative dose of rATG is 5–6 mg/kg, and the number of doses can vary, depending on graft function and white cell and platelet counts, but exceeding it is more likely to result in infective complications [4–6]. It is puzzling why the highest graft and patient losses were in the 2 induction groups, when the 'no induction' group had the highest AR. So, what caused the graft and patient losses?

The safety profile of rATG is impressive, with its use in 40% of inductions in LD transplants with a reduced incidence of AR and CMV infections [4,7,8], with nearly half of recipients not receiving steroids at 12 months, and 93.6% being free of AR at 5-year follow-up [4]. The logistic regression analysis in Table 3 shows rejection episodes to be a significant risk factor for CMV disease, yet, surprisingly, in Table 2, the low-risk group had less CMV disease despite a higher incidence of AR and required more immunosuppression. The authors claimed but were unable to show an association between fATG dose and CMV disease in Table 3. A beneficial effect not generally recognized is that by reducing DGF, rATG indirectly reduces the need for over-immunosuppression, with its inherent infective complications [3,9].

The paper is unconvincing because the data presented does not match the conclusions and the authors deviated from their primary objective. We feel that rATG, when used judiciously, is not only safe but is also key to improving graft and recipient outcomes.

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