

# ATG in allogeneic stem cell transplantation: standard of care in 2017? Counterpoint

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*This article has a companion Point by Bacigalupo.*

Despite improvements in HLA matching, quality control measures, and supportive care used in hematopoietic stem cell transplantation (HSCT), graft-versus-host disease (GVHD) remains a common cause of morbidity and mortality in transplant recipients.<sup>1</sup> The primary goal of HSCT is to cure the underlying hematological disorder with as little residual disability as possible. Achieving this goal requires supporting the patient through a conditioning regimen and its associated toxicity, opportunistic infections, and GVHD while avoiding relapse. Despite recognizing that donor T cells are critical in the establishment of both acute and chronic GVHD, it is important to remember that these cells also help in preventing opportunistic infections and providing a graft-versus-leukemia (GVL) effect when necessary. It was not surprising then that early on we discovered that ex vivo T-cell depletion could prevent or minimize GVHD, but at the cost of increases in mortality from rejection, relapse, and opportunistic infection.

It is generally accepted that preventing GVHD is more effective than treating it once it has been established. The use of antithymocyte globulin (ATG) reflects a form of in vivo T-cell depletion, which concomitantly depletes host T cells that have survived the conditioning regimen. This reduces the risk of rejection, while similarly depleting newly infused donor T cells, thus potentially reducing GVHD, GVL, and the passive transfer of memory T cells that reconstitute early immunity. An analysis of ATG's value is complicated by considerations of ATG formulation, sensitivity of the underlying disease to GVL, intensity of conditioning regimen, donor source, and other medications used for GVHD prophylaxis. The decision to use ATG must balance the circumstances in which ATG may be beneficial by reducing the incidence of GVHD with the situations in which ATG may be either neutral or harmful by increasing the risk of Epstein-Barr virus (EBV) posttransplant lymphoproliferative disease and other infections as well as relapse.

## Not all ATG formulations are the same

Although randomized controlled trials have demonstrated that ATG can reduce the risk of GVHD,<sup>2,3</sup> the differences in dosage and formulation of ATG make it difficult to generalize these results. For example, rabbit ATG (Thymoglobulin) is associated with more effective depletion of lymphocytes than horse ATG (ATGAM).<sup>4</sup> In addition to lymphocyte depletion, rabbit but not horse ATG enhances the number and function of regulatory T cells,<sup>5,6</sup> which are important in suppressing immune response and maintaining tolerance. The preservation or permissive expansion of regulatory T cells may limit GVHD after HSCT because these cells are needed for tolerance, controlling alloreactive donor lymphocytes involved in GVHD as well as innate and adaptive immune responses. These mechanistic differences between rabbit and horse ATG result in different outcomes in patients receiving immunosuppressive therapy or bone marrow transplantation for aplastic anemia.<sup>7,8</sup> There is yet another rabbit ATG formulation called anti-T lymphocyte globulin, ATLG Grafalon (Neovii), previously referred to as ATG-Fresenius, which is derived from the Jurkat T-cell leukemia cell line.<sup>9,10</sup> These different formulations do not have obvious dose equivalencies, and there is substantial interpatient variability. For example, the recommended dose in allogeneic HSCT for ATLG Grafalon is about 10 times that of Thymoglobulin, but they have not been compared clinically in head-to-head studies. The cytotoxicity to T cells with each ATG formulation has been demonstrated to be similar in an in vitro study, but it is unclear if the required ATG concentrations can be achieved in vivo to validate this analysis.<sup>11</sup> Furthermore, it is possible that the effect and outcomes with ATG are dependent on lymphocyte count at the time of infusion, and it is likely that an individualized approach to ATG dosing and timing could be beneficial to avoiding significant impairment in post-HSCT immune reconstitution.<sup>12-14</sup> In one interesting study, the serum from patients who underwent

HSCT with ATG showed that subpopulations of T lymphocytes (CD4, CD8) and natural killer cells (CD56) are selected that lose epitopes recognized by ATG, whereas B lymphocytes (CD20) and monocytes (CD14) maintain a homogeneity with respect to epitopes recognized by ATG.<sup>15</sup> How the antisera select for specific subpopulations of lymphocytes is unknown and further complicates our understanding of the mechanism of action as well as the variability of activity of ATG. This is in stark contrast to conventional pharmaceuticals that have more predictable effects. Without a clear understanding of the different specificities of these ATG formulations, and without head-to-head trials of different ATGs for GVHD prophylaxis, it remains difficult to draw any conclusions regarding the relative benefits or dosing of these 3 products.

### **ATG can increase infectious complications after HSCT**

Any therapy that can effectively reduce T cells in an allograft to reduce GVHD can also limit the ability of a stem cell transplant recipient to mount an appropriate T-cell immune response against infectious agents. Antithymocyte globulin clearly impairs immune reconstitution after HSCT and may also lead to delayed engraftment.<sup>10,16</sup> In the Canadian randomized phase 3 trial of rabbit ATG vs no ATG as part of HSCT conditioning, 33% of patients in the ATG arm had EBV reactivation compared with 3% who did not have ATG.<sup>2</sup> Patients with higher serum levels of ATG also have more EBV reactivation, but it is impossible to determine in advance what serum level to expect.<sup>17,18</sup> In an Italian study of 2 doses of ATG for GVHD prevention, patients receiving high-dose ATG had less GVHD, but no change in the incidence of treatment-related mortality resulting from increased infections in the high-dose ATG arm compared with the no-ATG arm.<sup>19</sup> This is consistent with other reports that demonstrate a difference in GVHD outcomes, but no difference in overall survival, likely because of increased infectious complications.<sup>3,10,20</sup> Viral infections are particularly difficult to manage after HSCT because there is often no effective antiviral therapy. For example, rituximab is useful for polymorphic EBV-posttransplant lymphoproliferative disease, but there is no therapy to eradicate the causative EBV. Rituximab failures may require EBV-specific cytotoxic T cells, but these are not yet generally available. Even bacterial infections are more common in patients receiving ATG.<sup>21</sup>

### **ATG could be compromising graft-versus-tumor activity**

Disease- and stage-related issues are critically important in understanding whether ATG influences relapse rates. For instance, dose intensity appears to be more important for early-stage, good-risk AML in which GVL seems less necessary.<sup>22</sup> This was also recently demonstrated in a randomized study of reduced vs myeloablative conditioning for patients with acute myeloid leukemia or myelodysplastic syndrome, in which the relapse rate was unacceptably high in the reduced intensity arm, closing the trial down earlier than expected.<sup>23</sup> It may be even more complicated than just reduced vs myeloablative conditioning. In a recently reported randomized trial of ATLG vs no ATLG in myeloablative HSCT, patients receiving cyclophosphamide and total body irradiation had significantly worse disease-free and overall survival when given ATLG vs those who did not receive it.<sup>10</sup> It is still too early to understand why this effect may have been observed, but this again illustrates that the use of ATG impacts relapse rates, even in patients receiving myeloablative conditioning. In a myeloablative phase 2 trial by the Blood and Marrow Transplant Clinical Trials Network in acute myeloid leukemia patients in

complete remission, 2 T-cell depletion strategies were combined (ATG and CD-34 selection). The incidence of grade 2-4 acute and extensive chronic GVHD were 23% and 7% at 24 months, respectively, and disease-free survival was 73% at 12 months. Thus, ATG and likely other T-cell depletion methods may be more beneficial in patients who do not rely heavily on GVL at the time of HSCT.

For diseases such as CML and low-grade lymphoma, the graft-versus-tumor effect is the driving force for inducing disease remission, in which case ATG has the potential to impair antitumor immunity after HSCT. In reduced intensity conditioning regimens, relapse rates are higher with ATG when compared with T cell-replete regimens in retrospective analysis, which suggested that a guarded approach to routine use of *in vivo* T-cell depletion with reduced intensity regimens is needed.<sup>24</sup> Caution in interpreting some phase 2 trials and retrospective studies is necessary, because there may be an interaction between ATG use and conditioning intensity, as physicians may choose myeloablative conditioning to offset the deleterious effects of ATG on relapse risk or vice versa.<sup>3,9</sup> None of the studies comparing ATG to no ATG has demonstrated a survival advantage with ATG, likely because of both increased infectious complications and relapse rates. Specifically with reduced intensity conditioning regimens, some survival data support a better outcome without ATG, suggesting the relapse risk overpowers the reduced GVHD risk.<sup>24</sup>

We therefore recommend an approach that takes disease risk, in addition to a conditioning regimen, into consideration when deciding about the use of ATG for GVHD prophylaxis. The disease risk index is a tool that uses type of malignancy and disease status at time of HSCT to quantify risk of relapse. Patients who have a high score at the time of HSCT are very likely to relapse,<sup>25</sup> and the attenuated GVL effect may not be justifiable. In patients receiving myeloablative conditioning who do not rely on GVL activity, the improved risk of GVHD with ATG is more acceptable. This may be the situation in which a transplant physician would accept the increased risk of infectious complications and delayed engraftment from ATG.

### **ATG in the landscape of other GVHD prophylactic strategies**

ATG is one of several strategies to deplete T cells at the time of HSCT to avoid GVHD, but it is unclear how this therapy compares with other forms of T-cell depletion. John Hopkins University pioneered a new approach to GVHD prevention using posttransplant cyclophosphamide in haploidentical HSCT that kills alloreactive T cells activated immediately after HSCT and spares regulatory T cells.<sup>26</sup> This strategy has led to acceptable rates of GVHD not only in haploidentical HSCT in which GVHD should be high because of the increased HLA mismatching between patient and donor,<sup>27</sup> but also in matched related and unrelated donor HSCT.<sup>28,29</sup> Posttransplant cyclophosphamide has been used in combination with a calcineurin inhibitor and mycophenolate mofetil, but has also demonstrated benefit as the sole GVHD prophylactic agent.<sup>28,29</sup> Although this strategy has become relatively mainstream in haploidentical donor HSCT, it remains controversial how posttransplant cyclophosphamide, alone or in combination with other GVHD prophylactic medications, will stack up to current standards of care. The concern with posttransplant cyclophosphamide, similarly to ATG, has been the high incidence of relapse in some of the earlier studies with this regimen. Another T-cell depletion approach that has effectively reduced GVHD rates is CD34 selection, which removes T cells

from the graft before stem cell infusion into the patient.<sup>22,30</sup> This strategy again offers a reduction in acute and chronic GVHD, but does not improve survival because of the increased infection-related deaths. Although ATG has been compared with standard GVHD prophylaxis strategies that include a calcineurin inhibitor and methotrexate, it is unclear if ATG is a better prophylactic strategy in comparison with these other T-cell depletion strategies.

## Conclusion

In the current era of HSCT, it is imperative to think about patients on an individual basis, assessing their risk of disease relapse, infection, and GVHD together. At present, we feel that the jury is still out regarding the role of in vivo T-cell depletion with one of the various ATG formulations. However, current data suggest reserving ATG for patients undergoing non-total body irradiation-based myeloablative conditioning with standard risk disease.

## Authorship

Contribution: N.K. and J.H.A. wrote and edited this manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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DOI 10.1182/bloodadvances.2016001552  
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