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Bone marrow transplant in aplastic anemia: the horse served us well, but is it still the best ride?

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Authors' contributions:

YBO and RR conceived the commentary, reviewed and interpreted the relevant literature, wrote and critically revised the manuscript, approved the final version, and agree to be accountable for its content.

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Aplastic anemia (AA) presents a relatively unique setting in the adult hematopoietic cell transplantation (HCT), with failure of the bone marrow, not because of cancerous or dysfunctional cells, but due to autoimmune destruction of early hematopoietic stem cells and stem cell progenitors. [1] Historically, because of the autoimmune and alloimmune nature of this disease,,graft rejection was the major obstacle to transplantation in AA, even in grafts derived from matched related donors (MRD).[2]

In this issue of Haematologica, Olivieri et al describe a retrospective analysis of 392 patients with AA treated with allogeneic HCT from MRD using mostly bone marrow grafts, in their institute, from the 1970s to 2024.[2] The analysis aimed to better define the role of horse-derived anti thymocyte globulin (hATG), in this setting. In the historical paper by Storb in 1974, hATG was indeed part of the original preparative regimen, combined with high-dose cyclophosphamide (200 mg/ m^2).[3] This protocol was a significant breakthrough, overcoming graft rejection, which had hitherto been the major obstacle, and thus enabled successful immunosuppressive therapy (IST) and transplants for AA, in the decades to come. As the authors state, the evolving practices of graft-versus-host disease (GVHD) prevention, particularly the immunosuppressive combination of cyclosporine A (CsA) and methotrexate (MTX), raise the question of whether hATG still provides meaningful additional benefit in this setting, although such considerations may not apply to rabbit ATG (rATG).[2]

The authors provide an important historical perspective of how the understanding of aplastic anemia, and thus its treatments, has evolved over the years, including the

rationale for incorporating ATG. There is a lack of randomized controlled trials, regarding ATG (of either source) in aplastic anemia, and some of retrospective studies did not differentiate between hATG or rATG, let alone between different dose regimens- a complexity that itself hampers decisive conclusions. And yet, through this retrospective analysis spanning several treatment eras, the authors imply that hATG might be redundant in AA transplantation from MRD using bone marrow grafts.

Horse ATG was introduced in parallel with major changes in GVHD prophylaxis, transfusion practice, and graft composition, all of which may have influenced transplant outcomes and complicates attribution of benefit to hATG alone. Since the different effects of hATG and rATG on the immune system, and the clinical implications of those differences, are relatively well substantiated, it is reasonable to consider these differences in a wider perspective to support better decision making.

Both, hATG and rATG differ fundamentally in their lymphodepleting effect, not only in depth and duration of immunosuppression, but also in the types of immune cells affected .[4] Rabbit ATG has a longer and deeper lymphodepleting effect, causing more infections in the long run when compared to hATG. It could have been assumed, as Scheinberg et al. predicted in 2011, that rATG would yield better results when used in the non-transplant frontline IST setting, but that was not the case.[5] Surprisingly, this RCT showed a clear advantage for hATG over rATG when given as frontline IST. Those results were further strengthened by a 2017 systematic review and meta-analysis as well as other registry studies. [5-6]

In contrast, when ATG was incorporated in conditioning for HCT, studies using rATG reported a clear advantage regarding GVHD prophylaxis.[6-7] It should be stated at this point, that these data are based on registry studies only, and no RCT compared rATG to hATG in that setting. Nevertheless, the consistent findings from the above-mentioned registry studies support continued consideration of rATG in the transplant setting and this approach has been reflected in the 2024 American Society for Transplantation and Cellular Therapy (ASTCT)AA consensus guidelines.[8]

The obvious question is why hATG appears to outperform rATG when used as part of IST, showing significantly better responses than rATG ? And why does rATG appear to have better outcomes than hATG when incorporated in conditioning prior to HCT? The answer may lie in the different effect each preparation exerts on the lymphocyte subsets, most importantly the CD4 T cells. CD4-cells are crucial for the recovery of hematopoiesis. When rATG is given as part of IST, deep CD4 suppression may impair autologous hematopoietic reconstitution, giving hATG a clear advantage. In contrast, when rATG is given as part of conditioning, hematopoietic recovery depends on donor stem cells, so the negative effect on the CD4 cells may matter less. In fact, this same CD4 depletion is likely one of the reasons rATG shows superiority in GVHD prophylaxis.[6,7,9,10]

Aplastic anemia differs from malignant indications for transplantation in one critical respect: there is no need for graft-versus-leukemia, and therefore no need to accept GVHD as a tradeoff for disease control. In this setting, GVHD is not a therapeutic mechanism but an unavoidable complication. The clinical objective should therefore be to reduce GVHD to the lowest possible level while preserving stable engraftment.

From that perspective, the message of Olivieri et al. is not necessarily that ATG should be abandoned altogether, but rather that hATG may no longer deserve a routine role in matched-sibling bone marrow transplantation for AA, whereas rATG still merits consideration if the goal is maximal GVHD prevention. Thus, the choice of ATG should depend on the clinical setting: hATG should be used for those patients receiving IST for AA without a transplant, whereas rATG remains an attractive option as part of conditioning, in the transplant setting. In view of the current data and mechanistic understanding, it is unlikely that such RCTs will be conducted. Meticulous attention to reports of current practice, perhaps focusing on differences in timing and dose of ATG, should be the cornerstone of further refinement of the immunosuppressive therapy in AA.

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Figure 1. Horse anti-thymocyte globulin versus rabbit anti-thymocyte globulin in aplastic anemia.

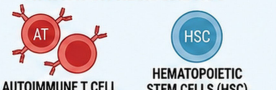
The figure summarizes the main mechanistic and clinical differences between horse anti-thymocyte globulin (hATG) and rabbit anti-thymocyte globulin (rATG), explaining their distinct roles in immunosuppressive therapy (IST; blue) and conditioning before allogeneic hematopoietic cell transplantation (HCT; purple).

HORSE VS RABBIT ATG - SIMILARITIES AND DIFFERENCES

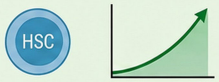
IMMUNOSUPPRESSIVE THERAPY (IST)
GOALS & ATG EFFECTS

DOMAINS REQUIRED FOR IMMUNOSUPPRESSIVE THERAPY

SUPPRESS AUTOIMMUNE ATTACK ON RESIDUAL HSC

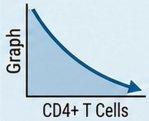


PRESERVE IMMUNE & HEMATOPOIETIC RECOVERY POTENTIAL



RABBIT ATG

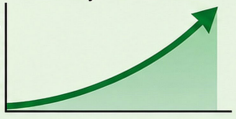
Immune System Effect



PROFOUND CD4+ T CELL LYMPHODEPLETION

HORSE ATG

Immune & Hematopoietic Recovery: PRESERVED



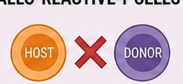
OVERALL CLINICAL OUTCOME WINNER

HORSE ATG is considered the superior choice for successful Immunosuppressive Therapy (IST) due to superior hematopoietic recovery and reduced infection risk.

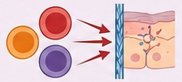
ALLOGENEIC HCT (ALLO HCT)
GOALS & ATG EFFECTS

DOMAINS REQUIRED FOR ALLOGENEIC HCT

ELIMINATE HOST ALLO-REACTIVE T CELLS



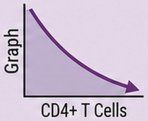
PREVENTION OF GVHD



(HOST RECOVERY CAPACITY IS IRRELEVANT)

RABBIT ATG

Immune System Effect

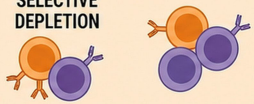


PROFOUND DEPLETION

HORSE ATG

Immune System Effect

SELECTIVE DEPLETION



OVERALL CLINICAL OUTCOME WINNER

HSC
T Cells
B Cells

RABBIT ATG is considered the superior choice for prevention of Graft-Versus-Host Disease (GVHD) and successful Allogeneic HCT.