Antithymocyte globulin and transplants for aplastic anemia

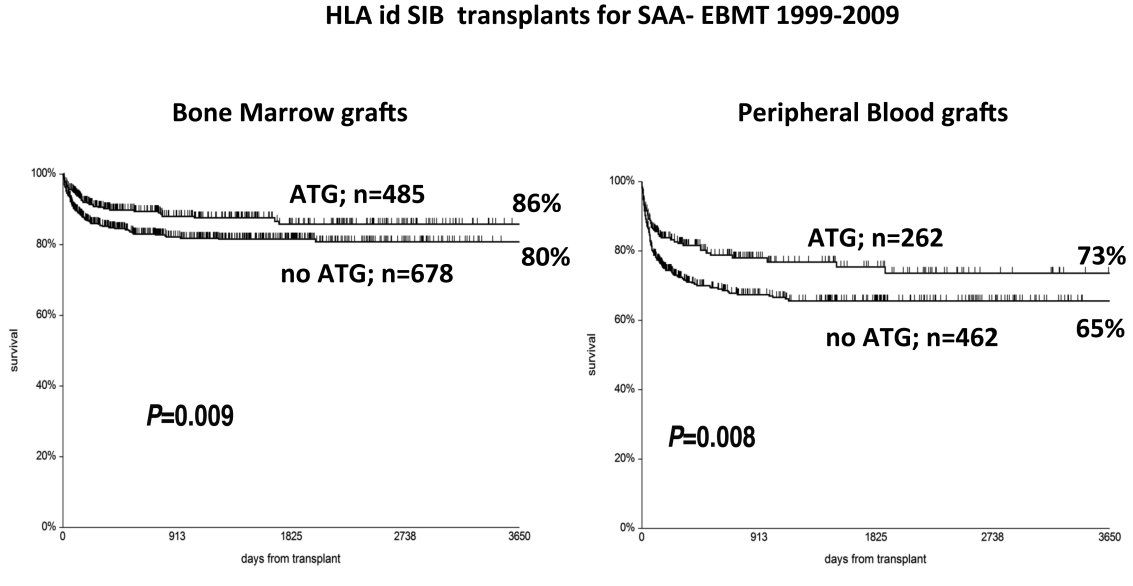
Andrea Bacigalupo

Istituto di Ematologia, Universita' Cattolica del Sacro Cuore, Fondazione Policlinico Universitario A Gemelli, Rome, Italy

E-mail: andrea.bacigalupo@unicatt.it *doi:10.3324/haematol.2017.171538*

In this issue of Haematologica, Kekre and colleagues have completed a study on the use of antithymocyte globulin (ATG) as part of the conditioning regimen for severe aplastic anemia (SAA) patients, undergoing an allogeneic stem cell transplant (HSCT) from matched sibling (MSD) or unrelated (UD) donors.[1] The Authors have found that rabbit ATG (thymoglobulin, Sanofi, France), as compared to horse ATG (ATGAM, Pfizer, USA) is associated with less acute graft-*versus*-host disease (GvHD), less chronic GvHD in MSD grafts, and improved survival in UD grafts, and recommend the use of rabbit ATG in the conditioning regimen for patients with SAA. The hypothesis for improved outcome of patients receiving rabbit ATG is that rabbit ATG is associated with more effective depletion of lymphocytes,[2] and that rabbit ATG, but not horse ATG, enhances the number and function of regulatory T cells,[3,4] which may be relevant in controlling GvHD and inducing tolerance.

Horse ATG was part of the original protocol designed by Storb *et al.*[5] for transplants from human leukocyte antigen (HLA)-identical siblings in SAA, together with cyclophosphamide (CY) 200 mg/kg. This protocol (CY200-ATG), followed by the infusion of unmanipulated bone marrow (BM) cells, was introduced more than 4 decades ago and is still considered the standard of care for young patients grafted from MSDs,[6] with survival exceeding 80% for these patients. However, several questions remain open, the first being whether we should continue to use ATG in 2017, especially as a prospective trial in 134 SAA patients failed to show a benefit for patients randomized to the horse ATG arm.[7] The study by Kekre and *et al.*[1] focused solely on patients receiving ATG, and thus we are missing the control arm. A registry-based study on HLA-identical sibling transplants (n=1886) showed a significant survival advantage for patients receiving ATG , irrespective of whether this was derived from horse or rabbit, both in univariate and multivariate analysis.[8] Therefore the answer to this first question is that ATG should be part of the conditioning regimen for SAA grafted from identical siblings, and the study by Kekre and colleagues[1] suggests



	ATG no	yes	P	ATG no	yes	P
aGvHD II-IV	13%	8%	0.005	21%	10%	0.0003
Ext cGvHD	4%	2%	0.1	9%	2%	0.001

Figure 1. MSD transplants for SAA - EBMT 1999-2009. Survival in patients with acquired aplastic anemia grafted from HLA identical siblings with bone marrow as a stem cell source (left) or with G mobilized peripheral blood (right). A significant survival advanatage is seen, together with less acute and chronic GvHD.HLA: human leukocyte antigen; MSD: matched sibling donor; EBMT: European Group for Blood and Marrow Transplantation; ATG: antithymocyte globulin; aGvHD: acute graft-*versus*-host disease; cGvHD: chronic graft-*versus*-host disease.

it should be rabbit ATG.

The second question is whether this holds true for patients receiving either BM or peripheral blood (PB) as a stem cell source? The answer is again yes, as shown in Figure 1, derived from the European Group for Blood and Marrow Transplantation (EBMT) data set 1999-2009.[8] The 10-year survival advantage is significant for both BM and PB, although it is more evident for patients receiving PB grafts , with a significant reduction of both acute and extensive chronic GvHD (Figure 1). Therefore a SAA patient grafted with BM from an identical sibling, with ATG in the conditioning regime, has an 86% chance of 10-year survival, with an 8% risk of acute GvHD and a 2% risk of extensive chronic GvHD; the same patient receiving a PB graft without ATG in the conditioning regimen has a 65% chance of 10-year survival, with a 21% risk of acute GvHD and a 9% risk of extensive chronic GvHD (Figure 1). This information may be useful when designing the transplant strategy for a given patient. A multivariate Cox analysis confirms that no ATG (P=0.0004) and PB grafts (P<0.00001) are two independent negative predictors of survival, together with age, interval between diagnosis and transplant and a conditioning other than CY200.[8]

The third question is whether ATG has a beneficial effect on survival, also for those SAA patients grafted from UDs? Again using data from an EBMT study,[9] the answer is yes: the 5-year survival rate of UD grafts with ATG (n=312) in 2005-2009 was 70%, compared to 52% for patients not given ATG in the conditioning regimen (n=198) (P=0.05). Once more this holds true in a multivariate Cox analysis, together with other independent predictors such as age, stem cell source and interval between diagnosis and treatment.[9] UD transplants pose additional problems, especially with engraftment and GvHD, and for this reason conditioning regimens currently include fludarabine and a small dose of total body irradiation (TBI) to increase immune ablation of the host.[10] The optimal dose of CY to be used in UD transplants, together with fludarabine, has also been the object of a recent study:[11] CY is recommended at the dose of 50 to 100 mg/kg, and TBI at the dose of 2Gy in a single fraction.[10,11] ATG would be used as a part of this conditioning regimen.

If ATG is a positive predictor of survival in both MSD and UD grafts, it may be relevant to identify the optimal dose and timing. Unfortunately, we do not have prospective studies comparing these two important variables, and the study by Kekre *et al.*[1] could not address this issue because the dose of ATG was not captured in the database. A conventional dose for thymoglobulin in transplants for SAA is between 5 and 7.5 mg/kg (total dose), administered in the 3 days before transplant; for ATGAM this would convert to a total dose of 120 mg/kg.

In conclusion, allogeneic HSCT for patients with aplastic anemia should always include *in vivo* T-cell depletion, irrespective of patients' age, donor type and stem cell source. We now have evidence that rabbit ATG (thymoglobulin) seems to protect patients from GvHD, better than horse ATG. The study by Kekre *et al.*[1] did not include patients receiving rabbit ATG-fresenius, so we do not have a comparison of this ATG with thymoglobulin and ATGAM. Another T cell depleting agent is alemtuzumab, which has been shown to achieve the same, if not superior protection against acute and chronic GvHD when compared to thymoglobulin in the transplant setting of SAA;[12] this may be particularly relevant in older SAA patients.

Given the unsatisfactory treatment of acute and chronic GvHD, and the lack of any benefit in SAA derived by the graft-*versus*-leukemia effect, particular care should be devoted to GvHD prophylaxis in patients with aplastic anemia. Stem cell source and *in vivo* T-cell depletion are modifiable transplant variables, and we now have evidence that the combination of BM stem cells and rabbit ATG provide optimal protection against GvHD, and may improve survival.

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