The Hemsphere Tribune

Updates and Insights on r-ATG in BMT

Individualizing rabbit anti-thymocyte globulin (r-ATG) exposure in every patient may be the key to overcoming the drawbacks of current weight-based r-ATG dosing strategies

Dose of r-ATG is pivotal in maintaining a balance.[1]

Timely T cell reconstitution

Preventing GvHD

Challenges related to the strategy:[2–5]

Weight-based r-ATG dosing strategies in HSCT patients[1–4]

- Poor T cell reconstitution
- Reduced graft-versus-leukemia effect and increased relapse and non-relapse mortality

The current weight-based dosing is empiric at its best!

Hence, there is a need for individualized r-ATG dosing for reducing exposure to r-ATG.

As per USFDA and EMA guidelines:[1]

Population pharmacokinetics modeling is required to determine an optimum individual r-ATG exposure.

Individualized optimum r-ATG exposure as determined by the pharmacokinetic modeling may hold the key to optimal patient outcomes with r-ATG dosing.[6,7]

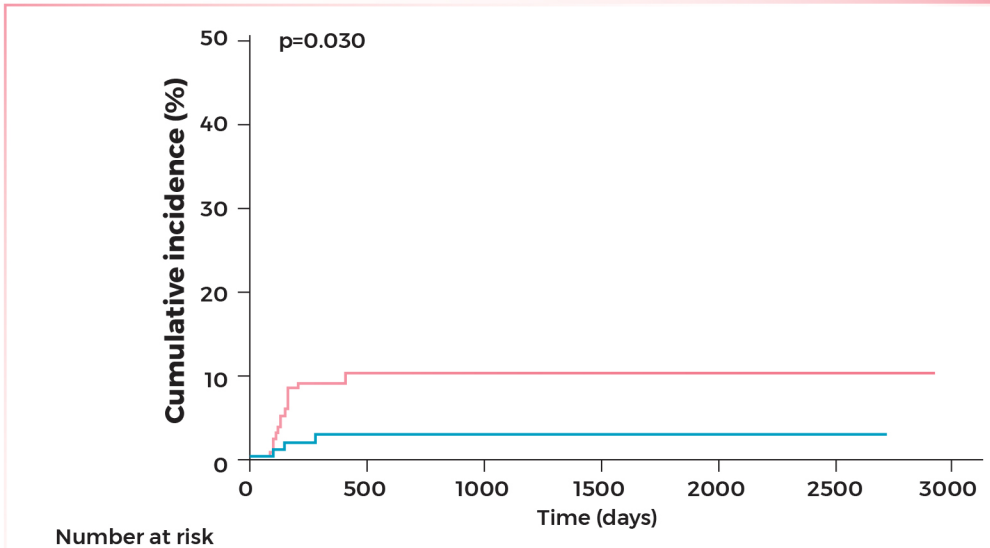
BMT: Bone marrow transplantation; EMA: European Medicines Agency; GvHD: Graft-versus-host disease; HSCT: Hematopoietic stem cell transplantation; USFDA: United States Food and Drug Administration.

Association between r-ATG exposure and CD4⁺ immune reconstitution[8]

AUC of r-ATG → Pharmacokinetic modeling studies and clinical trials demonstrate a strong relationship between the r-ATG exposure and T cell reconstitution[8] → **Immune reconstitution post-HSCT**

Study design and population	Outcome 1	Outcome 2	Conclusion
Retrospective analysis of pediatric aHSCT patients by Admiraal *et al.*[8] (N=251)	Reduced chance of successful immune reconstitution with increasing r-ATG AUC after aHSCT (odds ratio: 0.991; p<0.0001)	r-ATG AUC threshold minimum of 40 AU per day/mL significantly reduced aGvHD and cGvHD	Effective immune reconstitution increases OS and decreases NRM and relapse mortality

Cumulative incidence curves for graft failure according to AUC before transplantation[8]

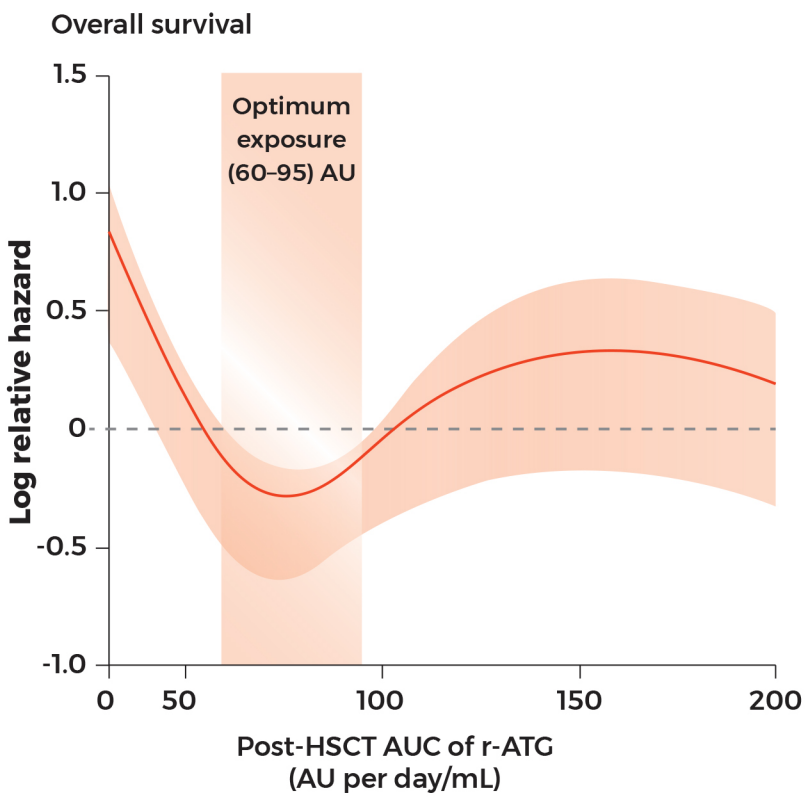


aGvHD: Acute graft-versus-host disease; aHSCT: Allogenic hematopoietic stem cell transplantation; AU: Arbitrary unit; AUC: Area under the curve; CD4⁺: Cluster of differentiation 4⁺; cGvHD: Chronic graft-versus-host disease; HSCT: Hematopoietic stem cell transplantation; NRM: Non-relapse mortality; OS: Overall survival; r-ATG: Rabbit anti-thymocyte globulin.

Association between r-ATG exposure and the 5-year overall survival outcome[1]

Retrospective analysis of 146 ALL, AML, and MDS patients[1]

Optimum r-ATG exposure post-transplantation= 60–95 AU per day/mL



Optimum r-ATG exposure after HSCT for favorable overall survival[1]

- Other outcomes
- Relapse mortality
- Non-relapse mortality

r-ATG exposure after aHSCT—**Best predictor of 5-year survival**

The model revealed that ALC-modeled dosing is better than weight-based dosing for optimal target exposure of r-ATG, especially in patients >50 kg.[1]

The model-suggested cumulative intravenous r-ATG dosage for optimal r-ATG exposure can be calculated using:[1]
Cumulative dose=400+350×lymphocyte count (in 10^9/L)

aHSCT: Allogenic hematopoietic stem cell transplantation; ALC: Absolute lymphocyte count; ALL: Acute lymphoid leukemia; AML: Acute myeloid leukemia; AU: Arbitrary unit; AUC: Area under the curve; BMT: Bone marrow transplantation; HSCT: Hematopoietic stem cell transplantation; MDS: Myelodysplastic syndrome; r-ATG: Rabbit anti-thymocyte globulin.

Prospective clinical evidences on individualization of r-ATG dose and aHSCT outcomes

PARACHUTE study[9]

aHSCT pediatric patients were treated with **individualized dosing regimen** based on body weight and ALC at the time of r-ATG initiation.

Primary endpoint: T cell reconstitution >0.05×10^9 $CD4^+$ T cells/L twice within 100 days [±3] after transplantation

Outcome[9]

ALC-based dosing regimen led to optimum r-ATG exposure in 97% vs. 30%–53% of the patients via weight-based dosing regimen.[9]

80% **of the subjects met the primary endpoint** within 100 days with individualized r-ATG dosing.

20% more than weight-based dosing from historical cohort

85% Other similar studies using **weight- and ALC-based r-ATG nomogram dosing** have achieved their primary endpoint.[10,11] 88%

Patients with inborn error of metabolism[10] — **T cell reconstitution in pediatric aHSCT** — Patients[11]

Single-centered prospective study[12]

Optimal active r-ATG exposure associated with the minimum risk of virus reactivation and grade II–IV aGvHD[12]

Adult patients with hematological malignancies undergoing haplo-PBSCT[12]

Wang *et al.* identified **that optimal active r-ATG 100–148.5 UE/mL/day is associated with the minimum risk of virus reactivation and grade II–IV aGvHD.**[12]

Conclusion: **Emerging clinical outcomes from attempts at individualizing r-ATG dose based on ALC±weight-guided r-ATG exposure are quite encouraging and lend credence to further evaluation attempts in the form of large-scale RCTs.**

aGvHD: Acute graft versus host disease; aHSCT: Allogenic hematopoietic stem cell transplantation; CD4+: Cluster of differentiation 4+; PBSCT: Peripheral blood stem cell transplantation; r-ATG: Rabbit anti-thymocyte globulin; RCTs: Randomized clinical trials.

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