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A Comparative Study of Various Formulations of Rabbit Anti-thymocyte Globulin for Graft *vs.* Host Disease Prophylaxis

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Abstract

Allogeneic hematopoietic stem cell transplantation is a potential curative therapy often employed for patients with haematological malignancies. Over the past two decades, numerous randomized controlled trials, reviews, and meta-analyses have investigated the effectiveness of rabbit anti-thymocyte globulin in preventing graft *vs.* host disease. However, only a limited number of these studies have aimed to compare different formulations of r-ATG. Given that the most recent article comparing various r-ATGs for GvHD prevention dates back to 2017, we conducted a systematic review of literature published from 2017 to the present using Indexed at, Scopus, Cochrane, and MEDLINE. Our primary focus was on acute GvHD (aGvHD) and chronic GvHD (cGvHD) prevention. We meticulously analyzed five studies in total; among these, four studies examined differences between Thymoglobulin (ATG-T) and Grafalon (ATG-G), while one investigated the impact of ATG-T dosage. Overall, the utilization of different r-ATG types does not appear to significantly influence cGvHD, aGvHD grades II–IV, transplant-related mortality (TRM), overall survival (OS), non-relapse mortality (NRM), leukemia-free survival (LFS), relapse rates, overall infection rates, and reactivation of the Epstein-Barr virus (EBV). However, conflicting data exists for aGvHD grades III–IV, graft *vs.* host-free survival (GRFS), moderate to severe cGvHD, and reactivation of the cytomegalovirus (CMV). Through our comprehensive research, our aim was to succinctly present the latest findings on r-ATGs in allo-HCT and provide insights into the distinctions among various ATG formulations in terms of their targets and origins.

Keywords: Anti-thymocyte globulin • Acute graft *vs.* host disease • Chronic graft *vs.* host disease

Introduction

Graft *vs.* host disease is a significant complication of allo-HCT (allogeneic hematopoietic stem cell transplantation), profoundly impacting the well-being and post-transplant life of patients. Factors such as elevated T cell count, HLA mismatch, and the use of peripheral blood stem cells (PBSC) as the primary transplant material have become vulnerabilities contributing to both acute (aGvHD) and chronic (cGvHD) forms. Despite administering calcineurin inhibitors (CNIs) along with methotrexate (MTX) for GvHD prevention, a considerable number of patients, ranging from 30% to 50%, experience aGvHD, while cGvHD persists in 30% to 70% of cases. Consequently, the focus is on devising effective immunosuppressive strategies that won't compromise post-transplant recovery [1].

In Europe, the prevailing GvHD prevention approach involves standard prophylaxis incorporating CNIs, MTX, or mycophenolate mofetil, combined with one of the available rabbit anti-thymocyte globulins (r-ATGs) for unrelated donor transplants, and more recently, for sibling donors as well. Different countries offer various ATG formulations derived from rabbits, horses, or pigs, generated by immunizing human cell lines or thymocytes. Horse ATG (h-ATG) and porcine ATG (p-ATG) are relatively uncommonly used in European nations. p-ATG is mainly employed for severe aplastic anemia in certain regions, and to a lesser extent, in allo-HCT contexts. Conversely, h-ATG is the primary therapy for moderate-severe aplastic anemia and GvHD prophylaxis [2].

Currently, there exist two types of rATGs, both composed of polyclonal IgG obtained from hyperimmune rabbit sera. These IgG antibodies are either immunized with human thymocytes for ATG-T (anti-thymocyte globulin, Thymoglobulin; Sanofi, Paris, France; formerly Genzyme), or with human Jurkat leukemia T-cell lines for ATG-G (anti-T-lymphocyte globulin, Grafalon; Neovii, Raperswil, Switzerland; formerly Fresenius). Moreover, ATG-T and ATG-G target different antigens. ATG-T binds to antigens expressed on T cells (CD2, CD3, CD4, CD6, CD8), B cells, natural killer cells, macrophages, dendritic cells, HLA class 1, and HLA-DR. ATG-T also includes antibodies targeting adhesion, trafficking, inflammation, apoptosis, and cellular proliferation-related antigens [3].

Description

The antigen recognition range of ATG-G is narrower compared to ATG-T, with fewer or no antibodies targeting CD3, CD4, or HLA-DR. However, ATG-G has more antibodies against CD107, an antigen expressed during T cell degranulation post antigenic stimulation. Competitive binding studies have demonstrated that ATG-T exhibits higher reactivity and a more potent complement-mediated cytotoxic effect on peripheral blood mononuclear cells than ATG-G. ATG-T induces dendritic cell apoptosis more effectively than ATG-G when equal doses are administered. Consequently, higher doses of ATG-G are used for GvHD prophylaxis. The immunological outcomes of ATG are also influenced by factors like cumulative dosage, timing of administration concerning allo-HCT, and recipient lymphocyte count during transplantation.

Higher ATG doses, closer administration to transplantation, and lower recipient lymphocyte counts can lead to prolonged ATG exposure following donor T cell infusion. This delays immune reconstitution, potentially increasing relapse risk, susceptibility to infections, and post-transplant lymphoproliferative disorder development [4]. Hence, these factors must be considered when assessing ATG administration outcomes. As recommended by experts, ATG-T and ATG-G are highly advised as part of myeloablative conditioning (MAC)

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before bone marrow (BM) and PBSC allo-HCT from matched or mismatched unrelated donors, to prevent aGvHD and cGvHD. Limited evidence also supports ATG-T and ATG-G before matched related donor (MRD) PBSC allo-HCT. Under reduced intensity or non-myeloablative conditioning (RIC/NMA) regimens, where higher relapse risks exist, ATG-T and ATG-G effectively prevent aGvHD and cGvHD. Studies demonstrate that ATG can reduce GvHD occurrence and extend survival in allo-HCT from unrelated donors (URDs) and haploidentical donors, without elevating relapse rates [5].

However, this article has several limitations. It lacks a network meta-analysis and a methodological quality assessment. Moreover, all included studies are retrospective, sometimes with relatively small sample sizes and uneven distribution of baseline patient characteristics. Despite this, the overall bias risk in the included studies is moderate. Thus, the data collected might not be entirely robust in establishing conclusions. To validate these findings, multicenter, large-scale, prospective, randomized controlled trials are still needed [6].

Conclusion

The particular form of rATG employed appears to have no substantial impact on overall cGvHD, aGvHD grades II-IV, TRM, OS, NRM, LFS, relapse, overall infections, and EBV reactivation. Nonetheless, there is incongruity in the findings regarding aGvHD grades III-IV, moderate-severe cGvHD, GRFS, and CMV reactivations. Beyond identifying the most suitable rATG formulation, the optimal timing, dosage, and blood concentration of rATG remain to be ascertained.

Acknowledgment

None.

Conflict of Interest

None.

References

1. Wingard, John R., Navneet S Majhail, Ruta Brazauskas and Zhiwei Wang, et al. "Long-term survival and late deaths after allogeneic hematopoietic cell transplantation." *J Clin Oncol* 29 (2011): 2230.
2. Martin, Paul J., George W Counts Jr, Frederick R Appelbaum and Stephanie J Lee, et al. "Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation." *J Clin Oncol* 28 (2010): 1011.
3. Pidala, Joseph, Brenda Kurland, Xiaoyu Chai and Navneet Majhail et al. "Patient-reported quality of life is associated with severity of chronic graft *vs.* host disease as measured by NIH criteria: Report on baseline data from the Chronic GVHD Consortium." *Blood J Amer Soc Hematol* 117 (2011): 4651-4657.
4. Watkins, Benjamin and Kirsten M Williams. "Controversies and expectations for the prevention of GVHD: A biological and clinical perspective." *Front Immunol* 13 (2022): 1057694.
5. Arai, Sally, Mukta Arora, Tao Wang and Stephen R Spellman, et al. "Increasing incidence of chronic graft *vs.* host disease in allogeneic transplantation: A report from the Center for International Blood and Marrow Transplant Research." *Biol Blood Marrow Transplant* 21 (2015): 266-274.
6. Flowers, Mary ED, Yoshihiro Inamoto, Paul A Carpenter and Stephanie J Lee, et al. "Comparative analysis of risk factors for acute graft *vs.* host disease and for chronic graft *vs.* host disease according to National Institutes of Health consensus criteria." *Blood J Amer Soc Hemat* 117 (2011): 3214-3219.

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