Regulatory T Cells and Ocular Graft Versus Host Disease: A Novel Treatment Approach

Mohammad Reza Pishnamaz 1*, Ebrahim Jafarzadehpour 1, Razieh Pishnamaz 2

1 Optometry Department, Iran University of Medical Sciences, Tehran, Iran
2 Department of Allergy and Immunology, Mashhad University of Medical Sciences, Mashhad, Iran

ABSTRACT

Graft Versus Host Disease (GVHD) is an inflammatory immune disease mediated by the donor’s immune cells and can arise after allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for the treatment of hematologic malignancies. It can lead to destructive manifestations in various tissues, particularly dermatological, gastrointestinal, and ocular tissues. The most common ocular morbidity is dry eyes, which is often the first manifestation of GVHD. Regulatory T cells (Tr) can be broadly classified as natural or adaptive (induced). After Bone-Marrow Transplantation (BMT), excessively increased levels of type 1 Tr (Tr1) are generally observed with absence of a GVHD, while low levels are seen with severe GVHD. Treatment of patients, undergoing BMT with Interleukin-10 (IL-10)-anergized donor T cells, led to immune reconstitution without the development of GVHD, which resulted in protection against infection and against the return of the cancer. Surprisingly, in both naive syngeneic mouse models of skin and cardiac allografts, graft retention was augmented after infusion of in vitro generated double-negative Tr (DN Tr). In addition, GVHD was reduced in mice with a genetic deficiency in the IL-27 receptor (IL-27R-/-) and in mice treated with anti-IL-27p28–specific antibody. Considering above mentioned findings we would suggest carrying out experiments, using animal models of GVHD, in order to evaluate the potential role of Tr, as an innovative approach to overcome severe ocular morbidity caused by ocular GVHD.

KEY WORDS

Graft vs Host Disease; T-Lymphocytes, Regulatory; Anti-IL-27p28–Specific Antibody; IL-27 Receptor

©2018, Med Hypothesis Discov Innov Ophthalmol. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial 3.0 License (CC BY-NC 3.0), which allows users to read, copy, distribute and make derivative works for non-commercial purposes from the material, as long as the author of the original work is cited properly.

INTRODUCTION

Graft Versus Host Disease (GVHD) is an inflammatory immune disease mediated by the donor’s immune cells, and can lead to the destruction of various host tissues [1]. Surprisingly, genetic dissimilarities between host and donor has proved to be ineffective for identification of auto-epitopes in this immune disease [2]. It can manifest either as acute or chronic GVHD (aGVHD and cGVHD, respectively), which are differentiated from each other according to their clinical manifestations. In 12% to 17% of patients with aGVHD, ocular manifestations occur, such as acute hemorrhagic conjunctivitis and pseudomembranous conjunctivitis. Exceedingly complex immunopathological mechanisms have been recognized for clinical features of cGVHD, and role of donor B and T cells besides other immune effector cells has been proven [3-5]. The GVHD can arise after allogeneic
Hematopoietic Stem Cell Transplantation (HSCT) for the treatment of hematologic malignancies. This occurs because of a reaction against allo-antigens on the surface of the recipient’s cells, similar to the beneficial graft-versus-tumor reaction, initiated by the donor’s immune cells against cancer cells [6, 7]. Once initiated, it can lead to destructive manifestations in various tissues, particularly dermatological, gastrointestinal, and ocular tissues. The most common ocular morbidity is dry eyes, which is often the first manifestation of GVHD. However, severe forms of GVHD can be lethal [4, 8].

Following the discovery of regulatory T cells (Tr), in 1995, as a subpopulation of CD25+CD4+T cells, immunologists suspected that these effector T cells had a suppressive role due to their expression of CD25. In 2003, the Forkhead Box P3 (FOXP3) transcription factor was identified as an essential marker of a subset of Tr that played a suppressive role in the immune system [9]. In general, Tr can be broadly classified as natural or adaptive (induced). Both of these cell types are responsible for preserving self-tolerance and preventing excessive immune responses against foreign antigens. After Bone-Marrow Transplantation (BMT), excessively increased levels of type 1 Tr (Tr1) are generally observed with absence of aGVHD, while low levels are seen with severe GVHD. Therefore, a growing number of trials have been investigating the potential role of Tr1 for both treating and preventing GVHD after BMT. To achieve this goal, treatment of patients undergoing BMT with Interleukin 10 (IL-10)-anergized donor T cells has been explored [10]. This treatment has been found to lead to immune reconstitution without the development of GVHD, which resulted in protection against infection and against the return of cancer [10].

In rodents, there is a special type of Tr, CD4 CD8 CD3+Tr, which is known as double-negative Tr (DN Tr). These cells exhibit unique surface markers, including CD69, CD45, CD30, CD62L, CD25, lymphocyte function-associated antigen 1 (LFA-1), T-cell receptor alpha/beta (TCRαβ), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Once activated, the cells can produce Tumor Necrosis Factor-alpha (TNF-α), Interferon-gamma (INF-γ), and Transforming Growth Factor-beta (TGF-β). In vitro and in vivo investigations have revealed the suppressive role of DN Tr on CD8+ and CD4+ T cell responses. Surprisingly, in both naive syngeneic mouse models of skin and cardiac allografts, graft retention was augmented after infusion of in vitro-generated DN Tr [11, 12].

In another animal study, GVHD was reduced in mice with a genetic deficiency in the IL-27 receptor (IL-27Rα) and in mice treated with anti-IL-27p28-specific antibody. Further investigations revealed that shifting the donor T-cell immune response away from pathogenic Tbet+CD4+type 1 T-helper cells and CD8+type 1 cytotoxic T cells, and towards CD4+ and CD8+ FOXP3-expressing Tr, significantly reduces GVHD grading in mice. In addition, an in vivo IL-27 blockade did not adversely affect IL-10 production by Tr and enhanced the stability of these cells during GVHD in mice [13]. Considering its evident efficacy in vitro and in animal models, a growing number of in vivo studies are currently applying Tr as a cell therapy in GVHD [14, 15].

**IMPLICATIONS**

Considering the above-mentioned findings, the current authors recommend carrying out experiments, using animal models of GVHD, in order to evaluate the potential role of Tr, as an innovative approach to overcome severe ocular morbidity caused by ocular GVHD.

**DISCLOSURE**

Ethical issues have been completely observed by the authors. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. No conflict of interest has been presented.

**REFERENCES**

1. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005;11(12):945-56. doi: 10.1016/j.bbmt.2005.09.004. PMID: 16338616

2. Mirza N, Zierhut M, Korn A, Bornemann A, Vogel W, Schmid-Horch B, et al. Graft versus self (GvS) against T-cell autoantigens is a mechanism of graft-host interaction. Proc Natl Acad Sci U S A. 2016;113(12):32. doi: 10.1073/pnas.1609118113. PMID: 27834728

3. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. Lancet. 2009;373(9674):1550-61. doi: 10.1016/S0140-6736(09)60237-3. PMID: 19282026

4. Anderson NG, Regillo C. Ocular manifestations of graft versus host disease. Curr Opin Ophthalmol. 2004;15(6):503-7. PMID: 15523196

5. Socie G, Ritz J. Current issues in chronic graft-versus-host disease. Blood. 2014;124(3):374-84. doi: 10.1182/blood-2014-01-514752. PMID: 24914139

6. Blaise D, Kuentz M, Fortanier C, Bourhis JH, Milpied N, Sutton L, et al. Randomized trial of bone marrow versus lenograstim-primed blood cell allogeneic transplantation in
patients with early-stage leukemia: a report from the Societe Francaise de Greffe de Moelle. J Clin Oncol. 2000;18(3):537-46. doi: 10.1200/JCO.2000.18.3.537 pmid: 10653869

7. Mohty M, Kuentz M, Michallet M, Bourhis JH, Milpied N, Sutton L, et al. Chronic graft-versus-host disease after allogeneic blood stem cell transplantation: long-term results of a randomized study. Blood. 2002;100(9):3128-34. doi: 10.1182/blood.V100.9.3128 pmid: 12384409

8. Ogawa Y, Okamoto S, Wakui M, Watanabe R, Yamada M, Yoshino M, et al. Dry eye after haematopoietic stem cell transplantation. Br J Ophthalmol. 1999;83(10):1125-30. pmid: 10502571

9. Li Z, Li D, Tsun A, Li B. FOXP3+ regulatory T cells and their functional regulation. Cell Mol Immunol. 2015;12(5):558-65. doi: 10.1038/cmi.2015.10 pmid: 25683611

10. Shalev I, Schmelzle M, Robson SC, Levy G. Making sense of regulatory T cell suppressive function. Semin Immunol. 2011;23(4):282-92. doi: 10.1016/j.smim.2011.04.003 pmid: 21592823

11. Zhang ZX, Yang L, Young KJ, DuTemple B, Zhang L. Identification of a previously unknown antigen-specific regulatory T cell and its mechanism of suppression. Nat Med. 2000;6(7):782-9. doi: 10.1038/77513 pmid: 10888927

12. Chen W, Ford MS, Young KJ, Zhang L. Infusion of in vitro-generated DN T regulatory cells induces permanent cardiac allograft survival in mice. Transplant Proc. 2003;35(7):2479-80. pmid: 14611991

13. Belle L, Agle K, Zhou V, Yin-Yuan C, Komorowski R, Eastwood D, et al. Blockade of interleukin-27 signaling reduces GVHD in mice by augmenting Treg reconstitution and stabilizing Foxp3 expression. Blood. 2016;128(16):2068-82. doi: 10.1182/blood-2016-02-698241 pmid: 27488350

14. Romano M, Tung SL, Smyth LA, Lombardi G. Treg therapy in transplantation: a general overview. Transpl Int. 2017;30(8):745-53. doi: 10.1111/tri.12909 pmid: 28012226

15. Zhang L, Yu J, Wei W. Advance in Targeted Immunotherapy for Graft-Versus-Host Disease. Front Immunol. 2018;9:1087. doi: 10.3389/fimmu.2018.01087 pmid: 29868032