Check for updates

Table 1. Granulocyte donor WNV infectious disease test results

Sample type	Collection date	WNV RNA TMA S/CO*	WNV IgM S/CO†	WNV IgG S/CO	WNV RNA by PCR in copies/mL‡
Index donation	8/9/10	29.53	NT	NT	700
Index retention	8/9/10	33.79	< 0.67	< 1.30	3600
Follow-up	10/18/10	0.02	4.73	3.74	< 5

TMA indicates transcription-mediated amplification; S/CO, signal-to-cutoff; PCR, polymerase chain reaction; and NT, not tested.

*TMA was done using the Gen-Probe/Novartis WNV assay on the TIGRIS automated platform. S/CO ratios of 1.00 or greater indicate a reactive test result.

†Antibody testing (IgM and IgG) was performed by Focus Laboratories. S/CO ratios of 0.67 or greater for IgM and 1.30 or greater for IgG indicate a positive test result.

‡PCR testing was performed by National Genetics Institute using a quantitative assay with a 95% lower limit of detection of 5 copies per milliliter.

The patient was readmitted and died on November 6 from complications of sepsis secondary to febrile neutropenia.

The multi-time donor is a 45-year-old man who received dexamethasone before donation. He was asymptomatic at donation, but subsequently became ill on August 22 with fever, chills, severe fatigue, headache, joint and bone pain, tremor, rash, and difficulty thinking. He was hospitalized on August 26 for treatment of WNV meningitis. His symptoms were consistent with those reported in WNV-infected donors.[6] He cleared his WNV infection and seroconverted at follow-up (Table 1).

Granulocytes must be transfused as soon as possible after collection and thus transfused before completion of infectious-disease testing.[7] The collecting facility performed WNV ID-NAT from August 3 through October 11 because of WNV activity in the area, consistent with recommendations in the United States.[3] The WNV infecting unit had a high viral load sufficient for detection by MP-NAT. Even though ID-NAT results are available sooner than those from MP-NAT, they were not available before the need for transfusion. The time required for generation of test results by any licensed screening test, including WNV NAT, prevents their availability before the need for transfusion of highly time-sensitive components. This case illustrates the need to evaluate the benefits of granulocyte transfusion for critically ill, neutropenic patients in the face of the rare possibility of WNV transmission during epidemic periods. Health care providers should be aware that granulocytes may transmit WNV, and thus health care providers should consider WNV as a potential cause of neurologic complications after granulocyte transfusion.

Geralyn M. Meny
American Red Cross, Penn-Jersey Region, Philadelphia, PA

Lauren Santos-Zabala
Monmouth Medical Center, Department of Pathology, Long Branch, NJ

Arpad Szallasi
Monmouth Medical Center, Department of Pathology, Long Branch, NJ

Susan L. Stramer
American Red Cross, Scientific Support Office, Gaithersburg, MD

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Dr Geralyn M. Meny, American Red Cross, Penn-Jersey Region, 700 Spring Garden St, Philadelphia, PA 19123; e-mail: menyg@usa.redcross.org.

References

1. Montgomery SP, Brown JA, Kuehnert M, et al. Transfusion-associated transmission of West Nile virus, United Sates 2003 through 2005. *Transfusion.* 2006;46(12):2038-2046.
2. Kightlinger L, Gorlin J, Kemperman MM, et al. West Nile virus transmission through blood transfusion–South Dakota, 2006.*MMWR Morb Mortal Wkly Rep.* 2007;56(4):76-79.
3. Stanley E, Ratard R, Staples JE, et al. West Nile virus transmission via organ transplantation and blood transfusion – Louisiana, 2008. *MMWR Morb Mortal Wkly Rep.* 2009;58(45):1263-1267.
4. Stramer SL, Fang CT, Foster GA, Wagner AG, Brodsky JP, Dodd RY. West Nile virus among blood donors in the United States, 2003 and 2004. *N Engl J Med.* 2005;353(5):451-459.
5. Biggerstaff BJ, Petersen LR. A modeling framework for evaluation and comparison of trigger strategies for switching from minipool to individual-donation testing for West Nile virus. *Transfusion.* 2009;49(5):1151-1159.
6. Zou S, Foster GA, Dodd RY, Petersen LR, Stramer SL. West Nile fever characteristics among viremic persons identified through blood donor screening. *J Infect Dis.* 2010;202(9):1354-1361.
7. Price TH. Granulocyte transfusion: current status. *Semin Hematol.* 2007;44(1):15-23.

Downloaded from http://ashpublications.net/blood/article-pdf/117/21/5779/1337554/zh802111005779.pdf by guest on 21 May 2024

To the editor:

Permissive, nonpermissive HLA-DPB1 epitope disparities and the specificity of T cells infiltrating the skin during acute graft-versus-host disease

Human leukocyte antigen (HLA)–DPB1 functions as a classic transplantation antigen.[1] In the context of hematopoietic stem cell transplantation (HSCT), when donor T cells recognize host HLA-DP, they can induce a graft-versus-host disease (GVHD) and/or a graft-versus-leukemia (GVL) effect, whereas in the opposite direction, host T cells recognizing the donor can induce rejection (HVG). Accordingly, any possibility to anticipate the nature and strength of an anti-DP T-cell response is crucial in this context.

Based on the HLA-DP recognition pattern of several HLA-DPB1*0901-specific T-cell clones, Crocchiolo et al classified HLA-DPB1 alleles according to their predicted "immunogenicity,"[2] and using an algorithm deduced from this classification (Figure 1), they showed that the presence of "nonpermissive" HLA-DPB1 mismatches correlated with a significantly increased hazard of acute grade 2-IV GVHD. Unexpectedly, the authors reported that the increased risk of aGVHD was detectable independently of the predicted direction (GVH/GVL or HVG) of the T-cell response. To reconcile the statistical observation with the immunologic hypothesis (the increased risk of GVH when the algorithm predicted the recognition of donor HLA-DP by host T cells), these authors considered the possibility of an indirect pathway for GVH because of cytokine release by host T cells recognizing "immunogenic" HLA-DPB1 on donor antigen-presenting cells (APC).

In 4 successive studies,[3-6] we have in the past assessed the specificities of T-cell clones infiltrating skin biopsies during aGVHD (Table 1). In each situation, T-cell clones specific for host HLA-DP were isolated from the skin at the onset of aGVHD. These studies demonstrated that no mismatch could theoretically be

Recipient DPB1 Group

1/1[a] 1/2 1/3 1/4 2/2 2/3 2/4 3/3 3/4 4/4

Donor DPB1 Group

1/1
1/1
1/3
1/4
2/2
2/3
2/4
3/3
3/1
4/4

Permissive
HvG
Permissive
GvH
Permissive
Perm

Algorithm for permissiveness of HLA-DPB1 mismatches in donor-recipients pairs.[2] Permissive and nonpermissive HLA-DPB1 disparity according to the algorithm described by Crocchiolo et al. [a]Numbers indicate the group of the 2 HLA-DPB1 alleles of the donor or the recipient. Group 1: DPB1*09:01,10:01,17:01; group 2: DPB1*03:01, 14:01, 45:01; group 3: DPB1*02:01, 0202, 0203; group 4: others.[3] Immunogenicity decreases from group 1 to group 4.

considered as "permissive," as confirmed in vitro by Rutten et al.[7] The finding of up to a 10-fold difference observed between frequencies of T cells directed at a "permissive" versus "nonpermissive" DP mismatch, as argued by Sizzano et al,[8] can hardly make a difference in the context of transplantation. T-cell frequency depends on the kinetics of the immune response and is a key physiologic factor in the race against an infection. In the present context of transplantation, the immune target (HLA-DP on host APC) remains present for weeks after the graft, and a 10-fold difference in frequency represents only 3-4 divisions for a T cell, which would take 1-2 days at most.

Nevertheless, a detailed analysis of anti-DP specificities remains particularly interesting and potentially useful (for example, to drive a GVL effect with DP-specific T-cell clones directed against an HLA-DP mismatch in the GVH direction, as we have previously proposed[3,4,9]). In line with HSCT, considering that "alloreactive TCR neither avoid contacting the bound peptide nor focus on the polymorphic residues that are exposed on the outer surface of the allo-MHC a-helices,"[10] it would be of great interest to learn more about the set of endogenous peptides presented by HLA-DP alleles in hematopoietic and nonhematopoietic tissues. This may help to improve the targeting of anti-DP allogeneic

Host-specific cytotoxic T cells against both permissive and nonpermissive HLA-DPB1 mismatches infiltrate the skin at the onset of aGVHD

UPN	Donor DPB1 (group)	Host DPB1 (group)	Mismatches in the GVH direction	Algorithm prediction of alloreaction	Skin-derived T-cell clones	Specificity
UPN2[5,6]	601/1001 (4/1)	401/1001 (4/1)	B2705, DR4, DQ8 **DP0401**	Permissive	HER-1, HER-28	**DP0401**
					HER-3, HER-30	B2705
					HER-27, HER-29	DQ8
UPN3[6]	0401/1901 (4/4)	1301/1901 (4/4)	A1, B17, DR0402 DQ8, **DP1301**	Permissive	P11	**DP1301**
					P1, P3, P6, P7, P10	DQ8
					P14	DR0402
UPN1[5,6]	0301/19 (2/4)	DP0101/19 (4/4)	A201, **DP0101**	HVG 0301 ←	A4, D2	**DP0101**
					TM15	A201
UPN5[3]	0401/0401 (4/4)	1001/0401 (1/4)	**DP1001**	GVH → 1001	BV2S1, BV6S7, BV14S1, BV17S1, BV8S1	**DP1001**
UPN4[4]	0301/0401 (2/4)	0401/0501 (4/4)	**DP0501**	HVG 0301←	BV6S7, BV8S1, BV13S1, BV17S1, BV22S1, BV5S2	**DP0501**

UPN1-5 are from References 3-6. Only case UPN5 fits the algorithm shown in Figure 1; most significantly, for UPN1 and UPN4 the T-cell reaction took place in the opposite direction of that expected by the algorithm. Data in bold indicate HLA_DPB1 mismatches in the GVHD direction.

UPN1: A 9-year-old boy with chronic myelogenous leukemia received a graft of his mother's bone marrow. The conditioning regimen consisted of cyclophosphamide (120 mg/kg) and total body irradiation (TBI): 12 Gy through 6 irradiation courses. GVHD prophylaxis consisted of cyclosporine A (CsA) and methotrexate (at days 1, 3, 6, and 11) and 5 mg/d of BB10, an anti–IL-2R antibody, for 10 days. GVHD was first suspected on day 13 and biopsy for culture performed at day 34. The patient died at day 99.

UPN2: A 7-year-old boy received a graft of his mother's bone marrow for acute myelogenous leukemia in the second complete response. The conditioning regimen consisted of TBI and high doses of cytarabine and melphalan. T-cell depletion was performed as GVHD prophylaxis using monoclonal antibody anti-CD2, anti-CD7, and rabbit complement. In addition, the patient received anti-LFA1 and anti-CD2 mAbs from day −3 to day 12. GVHD was suspected on day 19 and biopsy for culture at day 22. The patient died at day 120.

UPN3: A 10-year-old boy with idiopathic myelodysplasia and severe pancytopenia. After the patient failed to engraft with his mother's bone marrow, he received marrow from his father after the following conditioning regimen: busulfan 8 mg/kg over 2 days and cyclophosphamide 200 mg/kg over 4 days. The marrow was T cell–depleted with anti-CD2, anti-CD7, and rabbit complement. Additional in vivo immunotherapy with anti-LFA1 and anti-CD2 was performed as for UPN2. GVHD was diagnosed and skin biopsies performed at day 31 following the second transplantation. The patient died at day 89.

UPN4: A 48-year-old female with chronic myeloid leukemia received a graft from a donor from the French bone marrow transplant registry. Because of GVHD risk factors (patient age, advanced disease, and unrelated donor) and after informed consent, the patient received selected bone marrow (BM) $CD34^+$ cells with the aim of reducing GVHD risk through T-cell reduction. No other GVHD prophylaxis was used except $CD34^+$ selection. Only 3% $CD3^+$ T cells contaminated the CD34 preparation corresponding to a total number of T cells reinjected of 9.4×10^4/kg. GVHD was suspected and skin biopsy performed on day 10. The patient died at day 39.

UPN5: A 42-year-old male with Richter syndrome in first partial response was grafted with unmanipulated noncryopreserved marrow from a female donor. The conditioning regimen consisted of fractionated 12 Gy TBI with lung shielding at 8 Gy followed by cyclophosphamide 60 mg/kg for 2 consecutives days. GVHD prophylaxis consisted of cyclosporine A at a dose of 3 mg/kg/d, together with methotrexate 15 mg/m^2 on day 1 and 10 mg/m^2 on days 3 and 6. GVHD was diagnosed and biopsies performed at day 16. The patient died of aspergillosis at day 75. (See References 3-6 for details.)

Downloaded from http://ashpublications.net/blood/article-pdf/117/21/5779/1337554/zh802111005779.pdf by guest on 21 May 2024

reaction against the residual disease while avoiding the healthy tissues as much as possible.

Henri Vié
UMR892, Centre de Recherche en Cancérologie Nantes-Angers, Institut de recherche Thérapeutique, Nantes, France

Joëlle Gaschet
UMR892, Centre de Recherche en Cancérologie Nantes-Angers, Institut de recherche Thérapeutique, Nantes, France

Noël Milpied
Hématologie Clinique et thérapie cellulaire, Hôpital Haut-Lévêque, Pessac, France

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Dr Henri Vié, Inserm, 8 Quai Moncousu, 44007 Nantes Cedex 1, France; e-mail: hvie@nantes.inserm.fr.

References

1. Shaw BE, Mayor NP, Russell NH, et al. Diverging effects of HLA-DPB1 matching status on outcome following unrelated donor transplantation depending on disease stage and the degree of matching for other HLA alleles. *Leukemia.* 2010;24(1):58-65.
2. Crocchiolo R, Zino E, Vago L, et al. Nonpermissive HLA-DPB1 disparity is a significant independent risk factor for mortality after unrelated hematopoietic stem cell transplantation. *Blood.* 2009;114(7):1437-1444.
3. Gaschet J, Gallot G, Ibisch C, et al. Acute graft-versus-host disease after bone marrow transplantation with a single HLA-DPB1*1001 mismatch: involvement of different TCRBV subsets. *Bone Marrow Transplant.* 1998;22(4):385-392.
4. Gaschet J, Lim A, Liem L, et al. Acute graft versus host disease due to T lymphocytes recognizing a single HLA-DPB1*0501 mismatch. *J Clin Invest.* 1996; 98(1):100-107.
5. Gaschet J, Mahe B, Milpied N, et al. Specificity of T cells invading the skin during acute graft-vs.-host disease after semiallogeneic bone marrow transplantation. *J Clin Invest.* 1993;91(1):12-20.
6. Gaschet J, Trevino MA, Cherel M, et al. HLA-target antigens and T-cell receptor diversity of activated T cells invading the skin during acute graft-versus-host disease. *Blood.* 1996;87(6):2345-2353.
7. Rutten CE, van Luxemburg-Heijs SA, van der Meijden ED, et al. Both permissive and nonpermissive HLA-DPB1 mismatches can induce polyclonal HLA-DPB1 specific immune responses in vivo and in vitro [letter]. *Blood.* 2010; 115(1):151-153.
8. Sizzano F, Zito L, Crivello P, et al. Significantly higher frequencies of alloreactive CD4+ T cells responding to nonpermissive than to permissive HLA-DPB1 T-cell epitope disparities [letter]. *Blood.* 2010;116(11):1991-1992.
9. Ibisch C, Gallot G, Vivien R, et al. Recognition of leukemic blasts by HLA-DPB1-specific cytotoxic T cell clones: a perspective for adjuvant immunotherapy post-bone marrow transplantation. *Bone Marrow Transplant.* 1999; 23(11):1153-1159.
10. Housset D, Malissen B. What do TCR-pMHC crystal structures teach us about MHC restriction and alloreactivity? *Trends Immunol.* 2003;24(8):429-437.

Downloaded from http://ashpublications.net/blood/article-pdf/117/21/5779/1337554/zh802111005779.pdf by guest on 21 May 2024