associated with steroid responsiveness but is in linkage disequi-
rium with other SNPs, in either GR or another gene, which are in
turn responsible for this phenotype. In this regard, given the high
degree of genetic polymorphism at the GR locus, sequencing of the
entire GR gene, coupled with biochemical characterization of the
corresponding protein, will be necessary to determine whether
additional polymorphisms in the coding region that alter the protein
structure and/or transcriptional activity of GRβ may also affect
steroid responsiveness or other clinical features of these patients.
In conclusion, these data identify the first genetic link between
polymorphism of GR and the DBA phenotype, which may explain
the variegation of phenotype observed in this patient population.

Lilian Varricchio
Tisch Cancer Institute, Mount Sinai School of Medicine,
New York, NY

James Godbold
Tisch Cancer Institute, Mount Sinai School of Medicine,
New York, NY

Stuart A. Scott
Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine,
New York, NY

Carolyn Whitsett
Tisch Cancer Institute, Mount Sinai School of Medicine,
New York, NY

Lydie Da Costa
Service d’Hematologie Biologique, Hopital Robert Debre,
Paris, France

Dagmar Pospisilova
Department of Pediatrics, Faculty Hospital of Palacky University,
Olomouc, Czech Republic

Emanuela Garelli
Hematology Unit, Pediatric Department, University of Torino,
Torino, Italy

Paola Quarrelio
Hematology Unit, Pediatric Department, University of Torino,
Torino, Italy

Ugo Ramenghi
Hematology Unit, Pediatric Department, University of Torino,
Torino, Italy

Anna Rita Migliaccio
Tisch Cancer Institute, Mount Sinai School of Medicine,
New York, NY

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    CYP2C9, VKORC1, and CYP4F2 frequencies among racial and ethnic groups.

To the editor:

Tolvaptan inhibition of desmopressin effects on coagulation factors in a patient
with decreased von Willebrand factor and polycystic kidney disease

Desmopressin (dDAVP) is a synthetic analog of vasopressin that
stimulates release of von Willebrand factor (VWF). This effect is
attenuated in vitro by a type 2 vasopressin receptor (V2R)
antagonist.1 dDAVP is administered for prophylaxis and treatment
of bleeding in von Willebrand disease (VWD), mild hemophilia,
and chronic kidney disease (CKD).

In autosomal dominant polycystic kidney disease (ADPKD), cyclic
AMP promotes abnormal growth and proliferation of renal epithelium
that results in cyst formation and CKD.2,3 V2R inhibition attenuates
progression of CKD in rodent orthologs of ADPKD.4 Tolvaptan, a V2R
antagonist, is effective treatment for hyponatremia and is being evalu-
ated in clinical trials as treatment for ADPKD.4,5

Tolvaptan’s effects on dDAVP stimulation of VWF have not been
reported. We evaluated a 42-year-old man with ADPKD found
have low VWF levels during screening for a study of
tolvaptan treatment for ADPKD. A comprehensive bleeding his-
ory, using a standardized instrument,6 found no excessive bleeding
with several minor procedures, but revealed one episode of
hematemia from renal cyst hemorrhage and one episode of hemopty-
sis during an upper respiratory infection. Laboratory tests (Table 1)
were compatible with type 1 VWD or decreased VWF in the
case of blood type O.7,8 Mild thrombocytopenia and leukopenia
were attributed to splenomegaly, considered a consequence of his
ADPKD-associated polycystic liver disease. Thrombocytopenia
may have contributed to the prolonged platelet function analyzer
closure times (PFA).

dDAVP infusion, before treatment with tolvaptan (Table 1),
caused 2- to 3-fold increases in VWF antigen, ristocetin cofactor activity, and factor VIII coagulant levels, and normalization of PFA
and the activated PTT (aPTT). A dDAVP infusion was repeated
after 12 weeks of protocol treatment with tolvaptan (60 mg orally
every morning/30 mg orally every evening; Table 1). Comparing
pretolvaptan and posttolvaptan laboratory values before dDAVP
was administered showed no effect of tolvaptan on VWF
antigen, ristocetin cofactor activity, or factor VIII coagulant activity. In contrast, tolvaptan inhibited the previously observed
dDAVP-induced increases in VWF antigen, ristocetin cofactor activity, and factor VIII coagulant activity, and attenuated
correction of the aPTT and PFA. These effects were most likely
related to inhibition of V2R by tolvaptan. Epinephrine infusion
can stimulate VWF secretion even in the absence of V2R
activation.9 However, this alternative mechanism was not as-
sessed in our patient.

In conclusion, during treatment with tolvaptan, dDAVP may not
be sufficient for bleeding prophylaxis or treatment. This is a
concern in ADPKD, a major cause of CKD, where bleeding from
cysts and aneurysms has significant morbidity. Consequently, VWF
replacement may be required. Because the prevalence of individu-
als with levels of VWF below the conventional lower limit of
normal is estimated to be as high as 1%, and because tolvaptan is
prescribed for hyponatremia in patients with heart failure, cirrhosis,
and cancer and is potentially a treatment5 to slow the progression of
CKD in patients with ADPKD, our findings may be of general
importance.4,5,10 Evaluation of the responses to dDAVP is war-
ranted in patients with low VWF levels and these other conditions
during treatment with V2R antagonists.

<table>
<thead>
<tr>
<th>Table 1. Laboratory test responses to dDAVP before and during treatment with tolvaptan</th>
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<tbody>
<tr>
<td><strong>Before tolvaptan</strong></td>
</tr>
<tr>
<td><strong>VWF antigen, % (50%-150%)</strong></td>
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<tr>
<td><strong>PFA-100 collagen/epinephrine, s (74-186 s)</strong></td>
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<tr>
<td><strong>PFA-100 collagen/ADP, s (56-128 s)</strong></td>
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<tr>
<td><strong>VWF ristocetin cofactor activity, % (50%-125%)</strong></td>
</tr>
<tr>
<td><strong>Factor VIII coagulant activity, % (56%-172%)</strong></td>
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<tr>
<td><strong>Activated PTT, s (25-35 s)</strong></td>
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<tr>
<td><strong>VWF multimer</strong></td>
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<tr>
<td><strong>Factor XI coagulant activity, % (69%-155%)</strong></td>
</tr>
<tr>
<td><strong>Factor IX coagulant activity, % (69%-176%)</strong></td>
</tr>
<tr>
<td><strong>Prothrombin time INR</strong></td>
</tr>
<tr>
<td><strong>WBC, ×10^3/μL</strong></td>
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<tr>
<td><strong>Platelet count, ×10^3/μL</strong></td>
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<tr>
<td><strong>Serum LDH, IU/L</strong></td>
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<td><strong>BUN, mg/dL</strong></td>
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<td><strong>Serum creatinine, mg/dL</strong></td>
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<tr>
<td><strong>eGFR, mL/min/1.73 m²</strong></td>
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<tr>
<td><strong>MRI results</strong></td>
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dDAVP dose (0.3 μg/kg): blood samples obtained 30 minutes after dDAVP infusion. “During tolvaptan” blood samples obtained 2 hours after the morning dose of tolvaptan.
VWF indicates von Willebrand factor; PFA, platelet function analyzer; INR, international normalized ratio; WBC, white blood cell count; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate by Modification of Diet in Renal Disease formula; and MRI, magnetic resonance imaging.

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Jon D. Blumenfeld
The Rogosin Institute and the Department of Medicine,
Weill Cornell Medical College,
New York, NY

Jeffrey Tepler
Department of Medicine, Weill Cornell Medical College,
New York, NY

Andreas Mauer
The Rockefeller University,
New York, NY

Barry Coller
The Rockefeller University,
New York, NY

Daniel G. Bichet
Departments of Medicine and Physiology,
University of Montreal, Hôpital du Sacré-Coeur,
Montreal, QC

Barry Smith
The Rogosin Institute and the Department of Surgery,
Weill Cornell Medical College,
New York, NY

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**References**


**To the editor:**

**Successful mobilization and engraftment of PBSCs derived from donor cord blood cells after a previous allogeneic RIC single unrelated cord blood transplantation**

We describe a successful salvage treatment with intensive chemotherapy and stem cell transplantation for a relapse of Hodgkin lymphoma (HL) after single umbilical cord blood transplantation with a reduced intensity-conditioning regimen (RIC).1,2 The originality of this observation is the source of cells for the second transplantation; the grafted cells were obtained by the mobilization in the blood of stem cells (PBSCs) originating from the cord blood unit (CBU) used for the previous transplantation.

A 24-year-old patient was diagnosed with a nodular sclerosis classic HL (stage II Bb according to the Ann Arbor classification) in May 2007. A primary refractory disease was observed after 4 courses of adriamycin, bleomycin, vinblustine, and decarbazine (ABVD); 2 courses of mitoguazone, ifosfamide, vinorelbine, and etoposide plus rituximab (MINE-R); 2 courses of high-dose cytarabine (Ara-C), cisplatin, and dexamethasone (DHAP); and cervical irradiation (supplemental Table 1, available on the Blood Web site; see the Supplemental Materials link at the top of the online article). In August 2008, despite the availability of autologous stem cells and because of the chemotherapy refractoriness, we performed an allogeneic transplantation with RIC and a single unrelated CBU (6/6 HLA compatibility, 2.1 × 10^8 nucleated cells [NC]/kg, and 0.5 × 10^10 CD34+ cells/kg). RIC consisted of fludarabine (40 mg/m²/d on day −6 to day −2), cyclophosphamide (50 mg/kg/d on day −6), and a total body irradiation (2 Gy on day −1). Graft-versus-host disease (GVHD) prophylaxis associating oral mycophenolate mofetil (MMF; 1 g 3 times a day) and cyclosporine A (CsA; 4.5 mg/kg twice a day) was started on day −3. After thawing and washing, the viability of cells was 55%, the patient received 0.9 × 10^10 NC/kg and 0.3 × 10^10 CD34/kg. No grade ≥2 conditioning-related toxicity was observed; the patient received G-CSF from day +22 to day +25 and was discharged at day +25 after the graft. Neutrophils were > 1000/L at day +40 and platelets > 50 000/L at day +52 after transplantation. Grade IIa acute (day +29) and chronic GVHD (eyes and mouth) were treated with appropriate doses of corticosteroids. MMF was stopped at day +30 and CsA at day +240. Complete remission (CR) was confirmed at 3 and 9 months after CBU transplantation. Full donor chimerism was documented by quantitative PCR on day +40 and sustained until relapse at 16 months. A relapse occurred in January 2010; the patient received 3 cycles of salvage chemotherapy (GVD) between April and July 2010 (supplemental Table 1).

<table>
<thead>
<tr>
<th>Table 1. PBSC CD34+ cells collection</th>
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<tr>
<td><strong>1st apheresis (July 2010)</strong></td>
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<tr>
<td><strong>Separator</strong></td>
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<tr>
<td>Time collection, min</td>
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<tr>
<td>Volume treated, mL</td>
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<tr>
<td>Volume collected, mL</td>
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<tr>
<td>Circulating CD34+ cells, /mm³</td>
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<td>Total collection, × 10^8/kg</td>
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Correspondence: Jon Blumenfeld, MD, 505 East 70th St, New York, NY 10021; e-mail: jdblume@nyp.org.
Tolvaptan inhibition of desmopressin effects on coagulation factors in a patient with decreased von Willebrand factor and polycystic kidney disease

Jon D. Blumenfeld, Jeffrey Tepler, Andreas Mauer, Barry Coller, Daniel G. Bichet and Barry Smith