associated with steroid responsiveness but is in linkage disequilibrium 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 GR 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 variation of phenotype observed in this patient population.

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Contribution: L.V., E.G., S.A.S., and P.Q. performed experiments and analyzed data; J.G. performed the statistical analyses; U.R. provided the DNA from the patients and revised the manuscript; C.W., D.P., and L.D.C. revised the manuscript; A.R.M. designed research, analyzed data, and wrote the manuscript; and all authors have read the manuscript, concur with its content, and state that its content has not been submitted elsewhere.

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References


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 evaluated 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 to have low VWF levels during screening for a study of tolvaptan treatment for ADPKD. A comprehensive bleeding history, using a standardized instrument,6 found no excessive bleeding with several minor procedures, but revealed one episode of hematuria from renal cyst hemorrhage and one episode of hemopty sisis during an upper respiratory infection. Laboratory tests (Table 1)
were compatible with type 1 VWD or decreased VWF in the context 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 assessed 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 individuals 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 treatment 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 warranted in patients with low VWF levels and these other conditions during treatment with V2R antagonists.

**Table 1. Laboratory test responses to dDAVP before and during treatment with tolvaptan**

<table>
<thead>
<tr>
<th>Test</th>
<th>Screening</th>
<th>Before dDAVP</th>
<th>After dDAVP</th>
<th>Before dDAVP</th>
<th>After dDAVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>VWF antigen, % (50%-150%)</td>
<td>43</td>
<td>57</td>
<td>116</td>
<td>51</td>
<td>47</td>
</tr>
<tr>
<td>PFA-100 collagen/epinephrine, s (74-186 s)</td>
<td>225</td>
<td>245</td>
<td>111</td>
<td>244</td>
<td>211</td>
</tr>
<tr>
<td>PFA-100 collagen/ADP, s (56-128 s)</td>
<td>148</td>
<td>160</td>
<td>93</td>
<td>158</td>
<td>150</td>
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<tr>
<td>VWF ristocetin cofactor activity, % (50%-125%)</td>
<td>40</td>
<td>46</td>
<td>131</td>
<td>53</td>
<td>51</td>
</tr>
<tr>
<td>Factor VIII coagulant activity, % (56%-172%)</td>
<td>53</td>
<td>52</td>
<td>120</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td>Activated PTT, s (25-35 s)</td>
<td>33.7</td>
<td>35.5</td>
<td>29.4</td>
<td>35.0</td>
<td>34.3</td>
</tr>
<tr>
<td>VWF multimer</td>
<td>Normal</td>
<td>Normal</td>
<td>Larger than normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Factor XI coagulant activity, % (69%-155%)</td>
<td>89</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor IX coagulant activity, % (69%-176%)</td>
<td>79</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin time INR</td>
<td>1.0</td>
<td></td>
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<tr>
<td>WBC, ×10^3/μL</td>
<td>3.9</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hemoglobin, g/dL</td>
<td>13.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count, ×10^3/μL</td>
<td>121</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Serum LDH, IU/L</td>
<td>172</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.3</td>
<td></td>
<td></td>
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<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>64.3</td>
<td></td>
<td></td>
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<tr>
<td>MRI results</td>
<td></td>
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</tr>
<tr>
<td>Left kidney length, cm</td>
<td>21.3</td>
<td></td>
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</tr>
<tr>
<td>Right kidney length, cm</td>
<td>20.2</td>
<td></td>
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<tr>
<td>Total kidney volume, mL</td>
<td>1960</td>
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<td></td>
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<tr>
<td>Liver length, cm</td>
<td>22</td>
<td></td>
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<tr>
<td>Spleen length, cm</td>
<td>13.6</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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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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, vinblastine, and dacarbazine (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 \(\times 10^9\) nucleated cells [NC]/kg, and 0.5 \(\times 10^4\) CD34\(^+\) cells/kg). RIC consisted of fludara

References


Table 1. PBSC CD34\(^+\) cells collection

<table>
<thead>
<tr>
<th></th>
<th>1st apheresis (July 2010)</th>
<th>2nd apheresis (August 2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Separator</td>
<td>Cobe Spectra</td>
<td>Cobe Spectra</td>
</tr>
<tr>
<td>Time collection, min</td>
<td>182</td>
<td>183</td>
</tr>
<tr>
<td>Volume treated, mL</td>
<td>9011</td>
<td>8001</td>
</tr>
<tr>
<td>Volume collected, mL</td>
<td>161</td>
<td>166</td>
</tr>
<tr>
<td>Circulating CD34(^+) cells, /mm(^3)</td>
<td>44.1</td>
<td>28.8</td>
</tr>
<tr>
<td>Total collection, (\times 10^9) cells/kg</td>
<td>2.46 (2 bags)</td>
<td>1.85 (2 bags)</td>
</tr>
</tbody>
</table>

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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