To the editor:

Acquired high-titer factor VIII inhibitor: fatal bleeding despite multimodal treatment including rituximab preceded by multiple plasmaphereses

Acquired factor VIII (FVIII) inhibitors can cause life-threatening bleeding. Rapid restoration of coagulation is vital. Therapeutic approaches include factor substitution, immunosuppression (eg, steroids, cyclophosphamide), and plasmapheresis. A novel treatment option is rituximab, a chimeric monoclonal antibody targeting the CD20 antigen and blocking proliferation of normal B cells.

Recently, Wiestner et al reported on the reduction of acquired FVIII inhibitors in 4 patients by an immunosuppressive regimen including rituximab. Patients presented with FVIII activity (FVIIIc) ranging from less than 1% to 4% (normal range, 70%-200%) and inhibitor titers ranging from 5 to 60 Bethesda units (BU). In 3 patients, FVIIIc normalized after the first of 1 to 4 treatment courses. The inhibitor became undetectable within 3 to 12 weeks. Plasmaphereses were not necessary.

Here, we describe the clinical course of a patient suffering from acquired idiopathic FVIII inhibitors with extraordinarily high titer. The 71-year-old male was admitted for the development of a large painful mass in his left gluteal region. He had received an intramuscular injection for lumbalgia 4 days prior. Patient history included years of chronic obstructive pulmonary disease but was otherwise unremarkable, particularly for allergic diathesis. There was no family history of autoimmune diseases, bleeding disorders, or neoplasias. Clinical examination revealed a large painful mass in his left gluteal region and diffuse mucosal bleeding. Respiratory sounds were slightly prolonged; liver and spleen were not enlarged. Laboratory work-up demonstrated pathologic coagulation studies with a markedly prolonged activated partial thromboplastin time (aPTT) of 80 seconds, decreased FVIIIc of less than 1%, and high FVIII inhibitor titers of 633 BU. Extensive laboratory exams did not reveal further pathologic results.

After a 2-week treatment with steroids he was transferred to our unit with persistent bleeding (day 0, Figure 1). Here, the patient received one dose of FVIII inhibitor bypassing activity (FEIBA, Baxter BioScience, Heidelberg, Germany), followed by recombinant FVIIa (NovoSeven, NovoNordisk, Mainz, Germany) given for 3 days, which did not improve the clinical course. In need of rapid intervention, cyclophosphamide and vincristine were applied twice. At this point, as inhibitor titer had even increased to 19 800 BU, plasmapheresis was started. A dramatic decline in inhibitor titers was observed immediately thereafter (Figure 1). Yet, it is not reveal further pathologic results.

In 30% of patients, spontaneous resolution of acquired FVIII inhibitors has been described after an average of 21 months. However, in the case of bleeding and high antibody titers, rapid restoration of coagulation is required. This often is not achieved by current immunosuppressive regimen. With regard to novel treatment options, the successful application of 2-chloro-deoxyadenosine has recently been reported. Here, the median time to reach nadir inhibitor titers was 137 days; the median time for a 50% increase in FVIIIc was 117 days. Concerning efficacy of rituximab, data of Wiestner and colleagues suggest a faster FVIII recovery (3-12 weeks). Despite the promising treatment results with rituximab in several immunoglobulin-mediated disorders, it remains a concern whether the nadir of FVIII inhibitors can be achieved fast enough in high-risk cases.

To maximize treatment efficacy in our critically ill patient, we combined standard immunosuppressive therapy with plasmapheresis and rituximab. Plasmapheresis was intended to rapidly reduce autoantibody levels and allow for infusion of large amounts of plasma with procoagulant activities. Indeed, we experienced a decline in inhibitor titers after initiation of plasmapheresis. Within 25 days, a 200-fold reduction of inhibitors was achieved. Yet, it is...
of note that the remaining FVIII inhibitor titer of 94 BU still was high enough to cause fatal bleeding.

As the number of B cells at that time had already been markedly reduced, half-life of autoantibodies should be investigated.10 Whereas the combination of rituximab and plasmapheresis was effective in significantly reducing FVIII inhibitor titer, the autoimmune process with its enormous initial inhibitor burden was not overcome. Given the efficacy of combining rituximab with plasmapheresis, however, we strongly suggest its implementation in the very early clinical course in patients with extremely high antibody titers, when rapid elimination of antibodies is required to prevent fatal bleeding. This combined approach may be one way to solve the clinical problem of life-threatening bleeding upon FVIII inhibitors in the future.

Karl-Georg Fischer, Barbara Deschler, and Michael Lübbert

Correspondence: Karl-Georg Fischer, University Hospital Freiburg, Department of Medicine, Division of Nephrology and General Medicine, Hugstetter Str 55, D-79106 Freiburg, Germany; e-mail: fischer@med1.ukl.uni-freiburg.de

References


Response:

Rituximab in the treatment of acquired factor VIII inhibitors

The letter by Fischer et al highlights the clinical challenge presented by patients with acquired factor VIII (FVIII) inhibitors. Fatal bleeding remains a dreaded complication despite the availability of several hemostatic agents and a choice of immunosuppressive drugs. Their patient had an extremely high FVIII inhibitor titer and was treated initially with prednisone alone for 2 weeks, followed by combination chemotherapy, plasmapheresis, and 2 doses of rituximab. While there was a significant decline in inhibitor titer, the patient succumbed to bleeding complications 4 weeks after the start of polychemotherapy and 2 weeks after the initiation of rituximab. The 4 patients with autoimmune hemophilia that we reported had lower inhibitor titers (5 to 60 Bethesda units [BU]) at presentation. Following treatment with rituximab and plasmapheresis, however, we strongly suggest its implementation in the very early clinical course in patients with extremely high antibody titers, when rapid elimination of antibodies is required to prevent fatal bleeding. This combined approach may be one way to solve the clinical problem of life-threatening bleeding upon FVIII inhibitors in the future.

At this time we would certainly agree with Fischer et al that rituximab should be considered early in the management of patients with active bleeding and/or high titer FVIII inhibitors. In patients with very high antibody burden, it seems appropriate to use combination chemotherapy including prednisone, cyclophosphamide, and rituximab at the time of diagnosis. It is well known that FVIII inhibitors can resolve spontaneously in up to 30% of patients,5 and prednisone alone or in combination with cyclophosphamide will effect remissions in a substantial proportion of patients.6 However time to resolution of the antibody with these agents is usually slow, taking months, and prolonged treatment with prednisone and cyclophosphamide may be associated with significant side effects. If the response rate to rituximab continues to be confirmed, it is likely to be shown cost-effective in those patients who require factor replacement. A full course of 4 weekly doses of rituximab is less expensive than one day of replacement therapy with recombinant FVIII and a fraction of the cost of FVIIa (NovoSeven). In patients with low-titer inhibitors it may not even be necessary to give a full course of 4 doses of rituximab once a clear improvement has been detected.

Adrian Wiestner, Babette B. Wekaler, and Geraldine P. Schechter

Correspondence: Geraldine P. Schechter, VA Medical Center, 50 Irving St, NW, Washington, DC 20422-0001; e-mail: g.p.schechter@med.va.gov
Expression of the hemoglobin scavenger receptor (CD163/HbSR) as immunophenotypic marker of monocytic lineage in acute myeloid leukemia

The hemoglobin-haptoglobin scavenger receptor (CD163/HbSR) is a monocyte/macrophage-restricted transmembrane protein of the scavenger receptor cysteine-rich family. Antigen expression is related to monocyte/macrophage differentiation, with weak expression on peripheral blood monocytes and abundant expression on the majority of tissue macrophages. To clarify whether CD163/HbSR is also expressed on leukemic cells committed to the monocytic lineage, we measured cell-surface expression of CD163/HbSR on leukemic blast cells of 78 patients with acute myeloid leukemia (AML).

AML diagnosis was established by morphology and cytochemistry according to French-American-British (FAB) criteria and immunophenotyping. Cases were subclassified according to French-American-British (FAB) criteria and 6. Green D, Rademaker AW, Briet E. A prospective randomized trial of prednisone and cyclophosphamide in the treatment of patients with factor VIII autoantibodies. Thromb Haemost. 1993;70:753-757.

In conclusion, these results confirm early studies and demonstrate that CD163/HbSR is expressed not only on mature monocytes and macrophages but also on leukemic cells. We found the antigen exclusively on the majority of monocytic and a significant subset of myelomonocytic leukemias, suggesting that the restriction of CD163/HbSR expression to cells committed to the monocytic lineage is preserved beyond malignant transformation; this

To the editor:

Expression of the hemoglobin scavenger receptor (CD163/HbSR) as immunophenotypic marker of monocytic lineage in acute myeloid leukemia

The hemoglobin-haptoglobin scavenger receptor (CD163/HbSR) is a monocyte/macrophage-restricted transmembrane protein of the scavenger receptor cysteine-rich family. Antigen expression is related to monocyte/macrophage differentiation, with weak expression on peripheral blood monocytes and abundant expression on the majority of tissue macrophages. To clarify whether CD163/HbSR is also expressed on leukemic cells committed to the monocytic lineage, we measured cell-surface expression of CD163/HbSR on leukemic blast cells of 78 patients with acute myeloid leukemia (AML).

AML diagnosis was established by morphology and cytochemistry according to French-American-British (FAB) criteria and immunophenotyping. Cases were subclassified according to French-American-British (FAB) criteria and 6. Green D, Rademaker AW, Briet E. A prospective randomized trial of prednisone and cyclophosphamide in the treatment of patients with factor VIII autoantibodies. Thromb Haemost. 1993;70:753-757.

In conclusion, these results confirm early studies and demonstrate that CD163/HbSR is expressed not only on mature monocytes and macrophages but also on leukemic cells. We found the antigen exclusively on the majority of monocytic and a significant subset of myelomonocytic leukemias, suggesting that the restriction of CD163/HbSR expression to cells committed to the monocytic lineage is preserved beyond malignant transformation; this

Table 1. Correlation of CD163/HbSR expression with expression of other differentiation antigens, cytochemical stains, and plasma parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p (95% CI)</th>
<th>P</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD14</td>
<td>0.7495 (0.6283-0.8351)</td>
<td>&lt;.0001</td>
<td>78</td>
</tr>
<tr>
<td>CD15</td>
<td>0.2758 (0.0500-0.4747)</td>
<td>&lt;.015</td>
<td>78</td>
</tr>
<tr>
<td>CD33</td>
<td>0.3064 (0.0801-0.5026)</td>
<td>&lt;.008</td>
<td>76</td>
</tr>
<tr>
<td>CD64</td>
<td>0.7265 (0.5948-0.8202)</td>
<td>&lt;.0001</td>
<td>76</td>
</tr>
<tr>
<td>CDw65</td>
<td>0.4369 (0.2249-0.6094)</td>
<td>&lt;.0001</td>
<td>74</td>
</tr>
<tr>
<td>Unspecific esterase</td>
<td>0.3140 (0.0745-0.5193)</td>
<td>&lt;.01</td>
<td>68</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>0.6444 (0.4811-0.7645)</td>
<td>&lt;.0001</td>
<td>73</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>0.2815 (0.0514-0.4833)</td>
<td>&lt;.015</td>
<td>75</td>
</tr>
<tr>
<td>Transcobalamin II</td>
<td>0.3015 (0.0715-0.5011)</td>
<td>&lt;.01</td>
<td>74</td>
</tr>
</tbody>
</table>

Results from Spearman rank correlations are shown. CI denotes confidence interval.