Sirolimus for the Treatment of a Massive Capillary-Lymphatico-Venous Malformation: A Case Report
Aleksandar M. Vlahovic, MD, PhD, Natasa S. Vlahovic, MD, Emir Q. Haxhija, MD, PhD

Management of patients with complex vascular anomalies (VAs) is often associated with significant morbidity and mortality because of the lack of effective treatment modalities that may lead to significant improvement of the disease and/or healing. Recently, reports of treatment of patients with complex VAs with sirolimus revealed encouraging results. Sirolimus inhibits the mammalian target of rapamycin, which acts as a master switch of numerous cellular processes. We report a successful use of sirolimus for the treatment of a patient with a complex CLVM of the trunk and the right lower extremity believed to be untreatable. Our patient had 44 hospitalizations during the 10-year period, with various unsuccessful treatments and continuous deterioration of his clinical condition, ending up in a wheelchair. His condition reversed to normal everyday activities 9 months after initiation of sirolimus therapy. We conclude that sirolimus is a very promising therapeutic option for children with complex VAs of capillary-lymphatico-venous type.

The biological classification of vascular anomalies (VAs) clearly separates vascular tumors from vascular malformations. These 2 types of lesions have different clinical behavior and require different diagnostic and therapeutic strategies. There is a group of patients with very large VAs who are not amenable to treatment by surgical resection and/or other tissue destruction techniques and who end up with significant morbidity and mortality. This is why some authors use the term “complex” VAs for these patients. Recently, successful systemic treatment of such patients with sirolimus has been reported.

Sirolimus inhibits the mammalian target of rapamycin, which is a master switch of numerous cellular processes leading to cellular proliferation. Therefore, the rationale for use of sirolimus in treatment of children with complex VAs lies in its antiproliferative and antiangiogenic effects. We report about a patient with a massive capillary-lymphatico-venous malformation (CLVM) treated successfully with sirolimus after years of unsuccessful treatment with a number of different therapeutic modalities.

RESULTS
A boy was born at term after an unremarkable pregnancy of a 20-year-old primipara. After the delivery, it was noticed that the right gluteal region and the right lower extremity were edematous. A biopsy was taken from a masslike swelling of the right thigh and the lymphatico-venous malformation was found (Fig 1). The laboratory findings during the course of the disease are given in Table 1. At the age of 9 months after further enlargement of the right lower extremity, the diagnosis of a Klippel-Trenaunay syndrome was confirmed.
syndrome was proposed and the recommendation for continuation of the initiated physical therapy was given. In the following 5.5 years, the boy had 8 hospitalizations at the Physical Therapy Department for lymphatic massage therapy. However, the growth of the lesion was extremely progressive so that the right thigh of the child reached double the size of his left thigh (Figs 2A and 3A). Furthermore, MRI revealed the presence of a diffuse vascular malformation at the thoracic, abdominal, and pelvic cavities with infiltration of bony structures, which was originally reported as a “tumor” process (Fig 4A).

At the age of 6 years and 3 months, a further enlargement of the right lower extremity was noticed. This was associated with an episode of painful thrombophlebitis in the right lumbal region where large varicose veins were localized.

In the following 7 months, there were 9 hospitalizations. Subcutaneous treatment with interferon alfa 2b in doses of 3 million IU/m² of body surface area 3 times a week was initiated with antiangiogenic intent. Hospitalizations were needed for blood transfusions due to persistent anemia, and the follow-up examinations. MRI performed 11 months after initiation of interferon treatment showed further enlargement of the lesion.

Vincristine, actinomycin, and cyclophosphamide (VAC) CWS-96 protocol for soft tissue tumors was introduced as the next treatment option along with interferon. There were 8 cycles of VAC. After 6 months of treatment, MRI revealed a minimal regression of the lesion at the thoracic region. Interferon was discontinued after 17 months of treatment at the age of 8 years and 2 months.

There were additional 15 hospitalizations in the following 18 months, mainly due to blood transfusions and the follow-up evaluations. In addition, because of preputial enlargement caused by the growth of the CLVM, a circumcision was performed.

The child was 9 years and 7 months of age when propranolol was introduced as a single therapy in a dosage of 4 mg/kg body weight per day, with the intention to prevent further growth of the lesion. Because MRI did not show any relevant regression of thoracic and abdominal masses after nearly 3 months of treatment, this therapy was also ceased.

The interdisciplinary team consisting of pediatric hematopathologists, pediatric physical therapist, vascular surgeons, and plastic surgeons concluded that after 44 hospitalizations there were no more treatment options for this child. It was June 2012.

At the age of 10 years and 4 months the child was in a wheelchair with hip and knee flexion contractures, scoliosis, asymmetry of lower extremities, and he could not walk (Figs 2B and 3B). At this point, after repeated literature search and personal communications with experts, we decided to offer to our patient the treatment with sirolimus on the basis of compassionate use. Informed consent was obtained from both parents and the patient, and properly documented. Our institutional review board approved the review of patient’s medical record.

According to the instructions given, a starting per-oral dose of 0.1 mg/kg per 24 hours twice daily was begun with the aim of reaching the therapeutic range of 5 to 15 ng/mL, which has been previously reported in the literature. After treatment initiation, the morning blood level of sirolimus was 8.15 ng/mL. We

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**TABLE 1** Laboratory Findings During the Treatment of Our Patient

<table>
<thead>
<tr>
<th>Age</th>
<th>WBC</th>
<th>RBC</th>
<th>Hgb</th>
<th>Plt</th>
<th>Fibrinogena</th>
<th>D-dimersa</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 d</td>
<td>10.7</td>
<td>5.0</td>
<td>183</td>
<td>450</td>
<td></td>
<td></td>
<td>No therapy</td>
</tr>
<tr>
<td>1 mo and 7 d</td>
<td>8.4</td>
<td>4.6</td>
<td>113</td>
<td>652</td>
<td></td>
<td></td>
<td>Right femoral region biopsy</td>
</tr>
<tr>
<td>6 y and 6 mo</td>
<td>4.9</td>
<td>3.23</td>
<td>85</td>
<td>300</td>
<td>1.2</td>
<td>9925</td>
<td>Interferon α 2B</td>
</tr>
<tr>
<td>7 y and 6 mo</td>
<td>10.9</td>
<td>2.8</td>
<td>85</td>
<td>172</td>
<td>1.5</td>
<td>11 349</td>
<td>Interferon α 2B + VAC</td>
</tr>
<tr>
<td>9 y and 7 mo</td>
<td>5.16</td>
<td>3.41</td>
<td>91.0</td>
<td>110</td>
<td>0.9</td>
<td>14 325</td>
<td>Propranolol Circumcision</td>
</tr>
<tr>
<td>10 y</td>
<td>7.84</td>
<td>2.42</td>
<td>67.9</td>
<td>90</td>
<td>1.98</td>
<td>&gt;30 000</td>
<td>No therapy</td>
</tr>
<tr>
<td>10 y and 2 mo</td>
<td>5.74</td>
<td>3.36</td>
<td>88</td>
<td>147</td>
<td>1.4</td>
<td>3763</td>
<td>Rapamune</td>
</tr>
<tr>
<td>11 y</td>
<td>4.89</td>
<td>5.07</td>
<td>131</td>
<td>377</td>
<td>5.0</td>
<td>244</td>
<td>Rapamune</td>
</tr>
<tr>
<td>11 y and 9 mo</td>
<td>5.19</td>
<td>4.86</td>
<td>124</td>
<td>382</td>
<td>3.2</td>
<td>144</td>
<td>Rapamune</td>
</tr>
</tbody>
</table>

Normal values: WBC 4–10 000/mm³, RBC 3.8–6.0 million/mm³, Hgb 120–180 g/L, Plt 140–390 000/mm³, fibrinogen 1.69–3.92 g/L, D-dimers ≤250 ng/mL, Hgb, hemoglobin; Plt, platelets; RBC, red blood cells; WBC, white blood cells.

a Values for fibrinogen and D-dimers are missing for the ages of 6 days, and 1 mo and 7 days, respectively.
noticed a significant decrease in the size of the right lower extremity after 3 weeks of treatment.

Physical therapy was reinitiated 3 months after initiation of the treatment with sirolimus. One month later, the child began to walk again. The contractures of the right lower extremity and the equinus of the right foot resolved completely, and the scoliosis improved dramatically: after 8 months of treatment, the Cobb angle decreased from 23° to 5°. Although physical therapy was continuously a substantial part of the treatment of our patient, the contractures and the scoliosis resolved only after the massive CLVM started to decrease in size during sirolimus treatment. Nine months after the initiation of treatment with sirolimus, MRI showed an overall significant decrease in size of the CLVM (Figs 3C and 4B). Spinal nerve roots were also surrounded by the CLVM, the size of which also decreased after the sirolimus was initiated.

At the examination 18 months after the beginning of sirolimus treatment, the boy was 11 years and 10 months old and his laboratory findings were within normal range. He pursues completely normal everyday activities, including sports (Fig 2C).

DISCUSSION

Complex VAs with or without overgrowth are difficult to treat with currently available therapies. The treatment is often unsuccessful and may have significant side effects. Our patient has a diffuse, infiltrative lymphatic malformation as a part of the diffuse infiltrative CLVM, similar to the ones reported by Hammill et al and Reinglas et al. He had highly elevated D-dimers and a low fibrinogen, which are typical characteristics of a massive CLVM with localized intravascular coagulopathy in the venous part of the malformation. Because of the infiltrative growth pattern, size, and anatomic extent of the CLVM, we did not see the possibility for a successful surgical intervention or sclerotherapy treatment in our patient. The various systemic therapeutic modalities applied during the treatment course were mainly based on the experience gained during the treatment of our patients with hemangioma, hemangioendothelioma, and other soft tissue tumors. However, all these measures remained unsuccessful. Hammill et al reported that sirolimus may be a reasonable treatment option for complex VA when proven untreatable with other current treatment modalities. At present, there is only 1 published retrospective analysis of 6 patients with different VAs and 4 published case reports showing that sirolimus is a potent treatment option for patients with complex VA. In the case of our patient, sirolimus brought a spectacular improvement of his
condition and his everyday life. We cannot be sure of what was the exact mechanism for the complete reversal of contractures and the scoliosis seen in our patient. However, we speculate that this may be the result of the possible nerve decompression after significant reduction in size of the massive CLVM after initiation of treatment with sirolimus. With continuation of physical therapy, the condition of our patient improved.

After initiation of treatment with sirolimus, we followed our patient in monthly intervals in our outpatient clinic and regularly assessed the morning sirolimus blood levels and surveillance tests, consisting of complete blood cell count, analysis of plasma proteins and lipid status, urine analysis, and blood pressure measurements. We also obtained the history of patient’s everyday activities in the previous time period. After sirolimus was introduced, most laboratory findings normalized, anemia and thrombocytopenia resolved, and the signs of coagulopathy disappeared. There was no more need for blood transfusions. With the exception of a temporary, self-limiting hyperlipidemia, without any clinical relevance we did not record any other side effects of the treatment. We are, however, continuously monitoring our patient for most commonly reported negative side effects, such as stomatitis, headache, infections, myelodysplasia, acne, and hyperlipidemia. Although the long-term results of sirolimus treatment are lacking, so far, we do not see any other treatment option for our patient. He had 44 hospitalizations with various unsuccessful treatments and continuous deterioration of his clinical condition, ending up in the wheelchair. After 24 months of treatment with sirolimus, the child is in good condition, has normal laboratory findings, a significant involution of his complex VA, and he has returned to a normal everyday life. Our goals at the onset of sirolimus therapy were to reduce the size of the massive CLVM. We did not expect such an amazing effect ending up in a complete reversal of the morbidities caused by the underlying disease. The child is for the moment still on sirolimus, which we plan to taper gradually under strict monitoring of the size of the CLVM and the clinical behavior of his CLVM. In case of signs of disease recurrence, at present, we do not see any other option but to stay on sirolimus for a number of years to come under close monitoring. Our experience with successful use of sirolimus in a patient with a complex VA is supporting previous reports and encourages further research on this field.

ACKNOWLEDGMENTS

The authors thank Dr Gordana Samardzija from the Department of Medical Pathology for her assistance, and CEEPUS (Central European Exchange Program for University Studies) for their support.

ABBREVIATIONS

CLVM: capillary-lymphatico-venous malformation
VA: vascular anomaly
VAC: vincristine, actinomycin, and cyclophosphamide

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Pediatrics 2015;136:e513
DOI: 10.1542/peds.2014-3469 originally published online July 6, 2015;

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