Successful Treatment of Juvenile Polyposis of Infancy With Sirolimus

Veronica B. Busoni, MD,⁎ Marina Orsi, MD,⁎ Pablo A. Lobos, MD,⁎ Daniel D’Agostino, MD,⁎ Marta Wagener, MD,⁎ Paola De la Iglesia, MD,⁎ Victor L. Fox, MD⁎

Juvenile polyposis syndrome is a rare autosomal dominant condition characterized by multiple hamartomatous polyps throughout the gastrointestinal tract. Juvenile polyposis of infancy is a generalized severe form of juvenile polyposis syndrome associated with a poor prognosis. A 47-month-old female infant presented initially with gastrointestinal bleeding and protein-losing enteropathy at 4 months of age. At the age of 12 months, the condition worsened, requiring albumin infusions every 24 to 48 hours and red blood cell transfusions every 15 days. Upper gastrointestinal endoscopy, colonoscopy, and small-bowel enteroscopy revealed diffuse polyposis that was treated with multiple endoscopic polypectomies. Despite subtotal colectomy with ileorectal anastomosis, protein-losing enteropathy and bleeding persisted, requiring continued blood transfusions and albumin infusions. A chromosomal microarray revealed a single allele deletion in chromosome 10q23, involving both the PTEN and BMPRIA genes. Loss of PTEN function is associated with an increased activation of the protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway involved in cell proliferation. Treatment with sirolimus, an mTOR inhibitor, was initiated with the aim of inhibiting polyp growth. Soon after initiation of treatment with sirolimus, blood and albumin infusions were no longer needed and resulted in improved patient growth and quality of life. This case represents the first detailed report of successful drug therapy for life-threatening juvenile polyposis of infancy.
the scarcity of this condition and its high rate of mortality have limited the study of its molecular basis in the past.6

Mutation of the BMPR1A and PTEN genes are responsible for JPS and Cowden syndrome, respectively. The development of polyposis is a typical feature of both disorders. Microdeletions in chromosome 10q23 involving both contiguous genes are associated with aggressive polyposis in childhood.6 PTEN mutations are associated with several hamartomatous syndromes, including juvenile polyposis, Cowden syndrome, and Bannayan-Riley-Ruvalcaba syndrome, collectively named the PTEN hamartoma tumor syndrome.7 Associated extraintestinal manifestations include congenital heart disease, developmental delay, and macrocephaly.8

Morbidity associated with polyposis in JPS is significant. Standard treatment includes repeated endoscopic surveillance and polypectomy, with frequent need of red blood cell (RBC) transfusions and albumin infusions. Advanced nutritional support may be necessary in cases of severe growth impairment. In the most severe cases, colectomy may be necessary to reduce blood and protein losses.

CASE DESCRIPTION
A term (38 weeks’ gestation) girl delivered by cesarean delivery (weight 3300 g, length 49.5 cm, cephalic circumference 35.5 cm) presented at age 5 months with gastrointestinal bleeding and protein-losing enteropathy. Endoscopic examination, including upper gastrointestinal endoscopy, colonoscopy, and small-bowel enteroscopy, revealed diffuse polyposis (Fig 1 A–C). Repeated RBC transfusions and intravenous infusions of albumin were required despite multiple polypectomies performed during a series of endoscopic procedures (Table 1). Histopathology revealed characteristic features of juvenile polyps with no dysplasia in all resected polyps. Biopsies of grossly normal gastrointestinal mucosa showed normal histology (Fig 2). During laparotomy-assisted enteroscopy performed at 8 months of age, a major laceration of the mesentery was produced by traction during manipulation of the small bowel. A 15-cm jejunal resection with end-to-end anastomosis was performed with no later complications.

At the age of 12 months, the condition worsened, requiring albumin infusions every 24 to 48 hours to maintain an average albumin level of 1.4 g/dL. RBC transfusions were required every 15 days.

At 17 months of age, a subtotal colectomy with ileorectal anastomosis was performed during an emergent laparotomy for an ileocolonic intussusception. After this
procedure, protein-losing enteropathy persisted and requirements of blood transfusions and albumin infusion remained unchanged, presumably as a result of persisting protein exudation and bleeding from the gastric, small-bowel, and rectal polyps. Placement of a central venous catheter was required because of frequent blood sampling and albumin infusions.

The patient also had congenital abnormalities, including macrocephaly (head circumference >97th percentile) and complex congenital heart disease consisting of pulmonic stenosis and a ventricular septal defect.

A chromosomal microarray was performed, which revealed a 3078-Mb deletion in chromosome 10q23.2q23.31 involving both the PTEN gene and BMPR1A gene.

Given the difficulty to stabilize our patient and discharge her from the hospital, at 20 months of age, we decided to initiate treatment with sirolimus, an inhibitor of mTOR and the molecular pathway known to be activated in patients with PTEN mutations. An informed consent with detailed information about sirolimus and its uses in organ transplant, vascular anomalies, and PTEN disorders; the goal of therapy in JPI; and monitoring, risks, side effects, alternatives, and potential benefits was signed by the parents and physician. Our goal was to slow gastrointestinal polyp proliferation or, at least, favor their involution. Before starting treatment with sirolimus, the patient had an average albumin level of 1.5 g/dL, requiring albumin infusions every 24 to 48 hours. The clearance of α1 antitrypsin measuring protein exudation by fecal material was 176 mL/24 hours at initiation of treatment (normal value: <12.5 mL/day).

The initial dose was 0.8 mg/m² per day taken twice daily. After 1 month of treatment with sirolimus with a target serum level of 6 to 8 ng/mL, albumin infusions and RBC transfusions were no longer required. Albumin levels remained steadily 3.8 to 4 g/dL and hemoglobin levels over 12 g/dL. α1 antitrypsin clearance also improved to near-normal levels at 13.3 mL/day (Fig 3). Endoscopic evaluations showed a definite change in polyp growth, with scarce distribution and smaller size (Fig 1D–F). At 47 months of age, after 27 months of treatment with sirolimus, the patient remains stable with no transfusion requirements.

Congenital heart disease was treated through cardiac catheterization after gastrointestinal disease was under control at 22 months of age. Valvuloplasty was performed for pulmonic stenosis, with a residual gradient of 30 mm Hg. The interventricular communication was closed with a device with minimum residual shunt.

### TABLE 1 Endoscopic Procedures Before and After Sirolimus

<table>
<thead>
<tr>
<th>Age in Mo, Endoscopic Procedure Performed</th>
<th>No. Stomach Polyps (mean size, mm)</th>
<th>No. Duodenum Polyps (mean size, mm)</th>
<th>No. Jejunum Ileum Polyps (mean size, mm)</th>
<th>No. Colon Polyps (mean size, mm)</th>
<th>No. Resected Polyps</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>No</td>
<td>5 (15)</td>
<td>70</td>
<td>30 (15)</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>6 (5)</td>
<td>10 (15)</td>
<td>Not explored</td>
<td>49 (15)</td>
<td>38</td>
</tr>
<tr>
<td>17, subtotal colectomy (ileoectrectal anastomosis) performed</td>
<td>6 (8)</td>
<td>42 (15)</td>
<td>Terminal ileum 80 (7)</td>
<td>Rectum 20 (7)</td>
<td>65</td>
</tr>
<tr>
<td>19</td>
<td>4 (4)</td>
<td>14 (5)</td>
<td>Terminal ileum 56 (3)</td>
<td>Rectum 1 (2)</td>
<td>9</td>
</tr>
<tr>
<td>20, sirolimus treatment initiated</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>Terminal ileum 7 (3)</td>
<td>None</td>
<td>5</td>
</tr>
</tbody>
</table>
Since initiation of treatment with sirolimus, the magnitude of the enteropathy was reduced, and the patient could be discharged from the hospital without the need for central venous access 1 month post initiation of treatment. Edema resolved, and no albumin infusion or RBC transfusion was needed in the last 27-month follow-up interval. Post-treatment growth improvement was also evident (Fig 4). The patient and family’s quality of life improved by allowing the child to return home (300 miles from the hospital).

**DISCUSSION**

We believe that this is the first detailed report of successful drug therapy of this devastating and life-threatening condition. The child’s pretreatment and improved post-treatment clinical findings (laboratory values, growth parameters, and endoscopic findings) demonstrate a dramatic change in the natural evolution of this disease. The genetic defect underlying our patient’s condition is well defined by a deletion in chromosome 10q23 that includes the PTEN gene. The potential mechanism by which sirolimus works can be explained by its known inhibitory effect on the phosphatidylinositol 3-kinase/AKT/mTOR pathway involved in cell proliferation and regulated by PTEN.

As reported by Oliveira et al,9 patients with JPI are offered subtotal colectomy combined with intraoperative endoscopic removal of polyps as a palliative disease control. It is remarkable that despite multiple polyp resection or even subtotal colectomy, we were unable to obtain a decrease in the magnitude of protein loss. Sirolimus treatment improved severe protein-losing enteropathy in our patient and reduced the need for frequent infusions of albumin, with an evident improvement in her quality of life.

Sirolimus (originally named rapamycin) is an approved drug for suppression of the immune system after organ transplant and evidence suggests that use of mTOR inhibitors in children undergoing solid organ transplant is efficacious and safe.10 Its effect is produced by the inhibition of a protein called mTOR, a Ser/Thr protein kinase, which regulates cell growth and proliferation and is involved in the regulation of the immune system and the development of blood vessels and tissue growth. Sirolimus (and other mTOR inhibitors) are currently being used for the treatment of complex vascular malformations11 and different types of cancer, hoping that it will act on the abnormal development of blood vessels (angiogenesis). As an inhibitor of the mTOR pathway, an important regulator of cell proliferation and survival, sirolimus and its analogs have an expanding role in the treatment of tumors associated with tuberous sclerosis complex,12,13 lymphoproliferative disease, and autoimmune cytopenias.14,15

The etiologic basis for the subset of juvenile polyposis termed JPI is a contiguous PTEN and BMPR1A gene deletion.16 PTEN is a tumor suppressor gene whose function is frequently lost through genetic and epigenetic mechanisms. Loss of PTEN increases the activation of the AKT/mTOR pathway, which increases cell proliferation and survival and is associated with subsequent development of various tumors.

There is some preliminary evidence on the effect of sirolimus on cell proliferation in conditions with generalized polyposis. Hardiman et al17 reported experimental evidence of an inhibitory effect of rapamycin in a transgenic adenomatous polyposis coli mutation-dependent colon polyposis mouse model. The effect on polyps included a decrease in proliferation, an increase in differentiation, and prolonged time to development of dysplasia, resulting in increased animal survival.

Authors of several case reports have suggested a potential role in the treatment of patients with PTEN hamartoma tumor syndrome,18–21 and there is emerging experimental and clinical evidence for role in the treatment of adenomatous polyposis17,22 and Peutz-Jeghers syndrome.23–25

Although we are encouraged by the dramatic beneficial effect of sirolimus in our patient over a period of time exceeding 2 years, we remain cautious about predicting the long-term effects. The development of drug resistance...
remains a possibility, although this is not well described when used to treat other benign conditions. We also acknowledge that we are reporting a clinical response to sirolimus without direct evidence of its molecular effect on cells or tissue in our patient. Such evidence is beyond the scope of this report.

CONCLUSIONS

We report successful treatment of a child suffering from complications of severe infant juvenile polyposis using sirolimus. This treatment should be considered for other children who are similarly affected by this condition. Given the rareness of the disease, multicenter studies should gather experiences with multiple patients to explore the safety and long-term effectiveness of this drug therapy. This report contributes to the growing knowledge and experience of using inhibitors of the mTOR pathway for various conditions associated with tumor formation and cellular proliferation.

ACKNOWLEDGMENTS

We acknowledge a recent brief report in the form of a letter to the editor that was published after our manuscript was submitted for review. The authors reported a 5-year sustained positive response to sirolimus in a child with JPI.26

ABBREVIATIONS

AKT: protein kinase B
JPI: juvenile polyposis of infancy
JPS: juvenile polyposis syndrome
mTOR: mammalian target of rapamycin
RBC: red blood cell
REFERENCES


