

## Use of Oral Sirolimus in Paediatric Patients with Serious Vascular Anomalies: Case Report

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### Abstract

#### Background

Pediatric vascular anomalies comprise a heterogeneous group of clinical disorders of varying severity. These anomalies are divided into vascular tumors or vascular malformations. Different therapeutic strategies have been used depending on the pathology in question. In recent years, mammalian target of rapamycin (mTOR) inhibitors have been explored as a therapeutic option in patients with complex vascular anomalies that fail to respond to conventional therapies.

#### Case Report

Two patients affected by complicated vascular anomalies were treated with sirolimus. Case 1: fourteen-month-old male patient with primary congenital lymphedema in the right arm. Case 2: boy aged two years and eight months, diagnosed with a non-respectable cervical aposiform hemangioendothelioma (KHE). Both patients received sirolimus at doses of 0.8 mg/m<sup>2</sup>/12 h during 12 and 13 months respectively. Monitoring plasma sirolimus concentrations made it possible to safely deal with problems associated with the medication. Both patients experiment an important improvement of their pathology, maintained after suspending treatment. No adverse effects related to treatment with sirolimus were observed.

#### Conclusion

Oral sirolimus proved to be an effective strategy in the treatment of complicated vascular anomalies in our pediatric population.

**Key Words:** Pediatric Patients, Sirolimus, Vascular Anomalies.

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## 1- INTRODUCTION

Paediatric vascular anomalies comprise a heterogeneous group of clinical disorders of varying severity. Many of them are benign in nature, while others are complicated processes that can cause serious alterations, such as malformations, pain, and organ dysfunction (1). According to the classification of the International Society for the Study of Vascular Anomalies (ISSVA), updated in 2014, these anomalies are divided into vascular tumours or vascular malformations (2). Generally, vascular tumours are proliferative, and malformations enlarge due to the expansion of a developmental anomaly with no underlying proliferation. The growth and/or expansion of vascular anomalies can cause clinical problems such as disfigurement, chronic pain, recurrent infections, coagulopathies (thrombotic and haemorrhagic), organ dysfunction, and death (3). Individuals often experience progressive clinical symptoms with worsening quality of life.

Different therapeutic strategies have been used depending on the pathology in question: surgical treatment, corticoids, antineoplastic agents, interferon, thalidomide, or propranolol. In patients with complex vascular anomalies that fail to respond to conventional therapies, mammalian target of rapamycin (mTOR) inhibitors have been explored as a therapeutic option in recent years (4).

Sirolimus, also known as rapamycin, is an immunosuppressant whose approved use according to its safety data sheet is as prophylaxis for organ rejection in adult patients who have received a kidney transplant, with low to moderate immunological risk. It was approved by the Food and Drug Administration (FDA) in 1999 and the European Medicines Agency (EMA) in 2001. Its action mechanism is based on its combination with the specific cytosolic protein FKBP-12, forming the FKBP 12-sirolimus

complex, which inhibits the activation of the mammalian target of rapamycin (mTOR) molecule, a critical kinase for the progression of the cell cycle. The inhibition of mTOR results in the blocking of several specific signal transduction routes such as the expression of vascular endothelial growth factor (VEGF), regulating angiogenesis and lymphangiogenesis. As a result, by inhibiting the activation of mTOR, it blocks the protein synthesis route, and has an anti-tumour and anti-angiogenic effect (5, 6). Due to their anti-angiogenic effect, mTOR inhibitors are offering promising results in terms of their effectiveness and tolerability in the management of vascular anomalies, although few controlled trials are available (6).

## 2- CASE SERIES REPORT

### 2-1. Case 1

Fourteen-month-old male patient with primary congenital lymphedema in the right arm initially managed with rehabilitation treatment having ruled out surgical intervention due to difficult access. Following confirmation biopsy of a positive D2-40 lymphatic malformation, rehabilitation was halted and treatment commenced with Sirolimus at a dosage of 0.8 mg/m<sup>2</sup>/12 h.

After the first month of treatment, the patient showed a clear improvement in mobility due to a reduction in tension force, which continued throughout the whole of the treatment period. The patient's plasma Sirolimus concentrations were monitored during the treatment period, using a chemiluminescent microparticle immunoassay analytical technique. The mean plasma concentration was 11.32 ng/mL (range: 6, 27- 26, 19).

A deviation from the target range (5-15 ng/mL) was observed, related to a drug interaction due to concomitant treatment with azithromycin, an antibiotic prescribed

for a respiratory infection. The dose was adjusted to 0.4 mg/m<sup>2</sup>/day during the concomitance period, and the initial dose of Sirolimus was resumed on completion of treatment with the macrolide antibiotic. As a result of a further infectious process requiring treatment with antibiotics, treatment was temporarily halted, with a worsening of the oedema being noted after three days. After 13 months of treatment, the patient was positively re-evaluated for surgery, with a satisfactory outcome allowing treatment with Sirolimus to be suspended. No adverse effect associated with the treatment was observed.

## 2-2. Case 2

Male patient aged two years and eight months, diagnosed with a non-respectable cervical Kaposiform Hemangioendothelioma (KHE). The patient was treated with 23 cycles of vincristine (0.05 mg/kg/week), after corticoid treatment failed. Nine months after receiving the last cycle of vincristine, he was admitted to hospital with Kasabach-Merritt phenomenon (KMP), which initially responded to treatment with high-dose systemic corticoid therapy and dual antiplatelet therapy with acetylsalicylic acid and ticlopidine. During the process of reducing the corticoid treatment, the patient had to be readmitted due to KMP. He initially had a platelet count of  $11 \times 10^9/L$  (reference value:  $130-450 \times 10^9/L$ ), which descended over the following two days to  $6 \times 10^9$  platelets/L.

After failing to respond to the previous treatment, it was decided to add Sirolimus to the dual antiplatelet therapy at a dose of 0.8 mg/m<sup>2</sup>/12 h, and to subsequently adjust it based on pharmacokinetic monitoring. Following 5 days of treatment, the patient's platelet values returned to normal, remaining within range throughout the entire treatment. The patient initially received a Sirolimus dose of 0.8 mg/m<sup>2</sup>/12 h, obtaining a mean plasma concentration

(using the chemiluminescent micro-particle immunoassay technique) of 9.86 ng/mL (range: 3.49-17.8). After 72 days of treatment, a hypertriglyceridemia secondary to treatment with Sirolimus was observed (triglyceride value: 306 mg/mL; reference value: 30-200 mg/mL), as a result of which it was decided to reduce the dose to 0.8 mg/m<sup>2</sup>/24 h. The patient's triglyceride levels returned to normal 41 days after reducing the dose. No decrease in effectiveness was observed following this reduction. The mean plasma concentration with the dose of 0.8 mg/m<sup>2</sup>/24 h was 3.73 ng/mL (range: 2.9- 4.95). After 388 days of treatment, it was decided to suspend the administration of Sirolimus and to carry out regular controls. At present, the patient's platelet count is still within range, one year after halting the treatment. No other adverse effect associated with the treatment was observed.

## 3- DISCUSSION

Lymphatic malformations are the second most frequent type of vascular malformation after venous malformations. They are more commonly located in the head and neck (70-80%), usually in the posterior cervical triangle. The remaining 20% may be located in the axillary, superior mediastinal, mesenteric or retroperitoneal areas, the pelvis and the lower limbs. It has been demonstrated that medical treatment with antiangiogenic agents is effective in very extensive, diffuse malformations, especially in newborn infants with extensive cervicofacial lesions. In many cases, this treatment is usually associated with percutaneous management of lesions, or even an additional surgical resection (7).

Kaposiform hemangioendotheliomas are infiltrative lesions that invade skin, subcutaneous fat, and muscle planes. KHE can cause a coagulopathy called Kasabach-Merritt phenomenon with

platelet trapping resulting in profound thrombocytopenia, enlargement of the lesion, and a consumptive coagulopathy with significant hypofibrinogenemia, which has a mortality rate of 14–24%. Steroids are often used as first-line therapy with varying results, and vincristine is generally used as second-line therapy once steroid treatment has proven insufficient (1). Our patients, both of whom have complicated vascular anomalies, responded well to Sirolimus, a drug with a narrow therapeutic range, which means its plasma concentrations should be monitored. A plasma concentration of 5-15 mg/ml was set as the target range, based on the available literature, which suggests that these values are sufficient in vascular anomalies (1, 3, 6).

For different reasons, both of our patients deviated from these values: in case 1, the target plasma concentrations were exceeded due to a drug interaction with azithromycin. Sirolimus is a macrolide antibiotic formed by a ring with one lactone and one lactam group, produced through fermentation by the actinomycete *Streptomyces higroscopicus*. Azithromycin can increase its levels, by interfering in its elimination by competing as a substrate of glycoprotein-P (MDR1 transporter). In case 2, it was decided to reduce the dose after detecting hypertriglyceridemia as an adverse effect associated with Sirolimus (an adverse effect indicated on the safety data sheet of Sirolimus as very frequent,  $\geq 1/10$ ) (1, 3).

Sirolimus does not have any approved indication on its safety data sheet for use in minors under the age of 18, or for the treatment of vascular anomalies. Experience in the use of Sirolimus administered orally in paediatric patients is limited: a number of studies have endorsed its possible benefits in paediatric patients with vascular anomalies, although no standard criteria has been defined for its conditions of use, dosage, or the

monitoring and duration of the treatment. Clinical trials in paediatric patients are required in order to design a clinical protocol based on the evidence, which makes it possible to define optimal posology guidelines in these patients, design the most appropriate monitoring model, and manage its safety profile. The limitations of the study are due to the fact that it is a retrospective descriptive observational study, based on a review of clinical records, with a small sample size.

We believe that once the decision has been made to begin treatment with oral Sirolimus, it is essential to closely monitor its plasma concentrations, as it is a drug with a narrow therapeutic range. In our case, this monitoring allowed us to identify an interaction between Azithromycin and Sirolimus that was not included in any of its safety data sheets (5, 8).

#### 4- CONCLUSION

Oral Sirolimus proved to be an effective strategy in the treatment of complicated vascular anomalies in our paediatric population. Monitoring plasma Sirolimus concentrations made it possible to safely deal with problems associated with the medication. No serious effect associated with the treatment was observed.

**5- CONFLICT OF INTEREST:** None.

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