suPERficial Slow-flow Vascular malFORMations Treated With sirolimUS (PERFORMUS): résultats préliminaires.

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Background – Inhibitors of mTOR (mammalian target of rapamycin), especially sirolimus, are increasingly used for treating various vascular anomalies in adults and children, due to their anti-angiogenic and -lymphangiogenic properties. Evidence is needed to allow for delineating when and how sirolimus should be used.

Objectives – We aimed to perform a randomized clinical trial to assess the efficacy and safety of sirolimus in complicated superficial slow-flow vascular malformations (SVMs) in children.

Methods – We conducted an open-labelled, phase 2, randomized observational-phase designed trial, that involved 12 French tertiary hospital centers for vascular anomalies, from September 2015 to March 2019. After enrollment (M0), patients first underwent an observational period, then switched to an interventional period when they all received sirolimus (0.08 mg.kg, to reach target levels 4 to 12 ng/ml). The switch time (MS) was randomized from month 4 to month 8, and the whole participation to the study lasted 12 months for each patient. Participants were children aged between 6 and 18 years, with a SVM (venous, lymphatic or combined), with no contra-indications to sirolimus and to RMI. They underwent 3 RMI, at M0, MS and M12. The primary outcome was relative changes of the SVM volume related to the duration period (between the observational and the interventional periods), with a centralized interpretation of RMI by a radiologist, blinded from treatment period. Secondary outcomes included subjective assessments of efficacy, pain, quality of life and safety.

Results – A total of 63 participants were enrolled, among whom 59 were included in the intended to treat analysis. The mean age ± standard deviation was 11.6 years ± 3.8, and 59.3% (n=35) were females; 22 subjects (37.3%) had a venous malformation (VeM), and 37 (62.7%) a VM with a lymphatic component (LM). The median volume of the VeMs and LMs were respectively: 128.25 and 182.52 mm^3 at M0; 110.40 and 283.50 mm^3 at MS; 134.65 and 151.20 mm^3 at M12. Variations of volumes related to the period durations showed no significant decrease from observational to interventional periods. However, when self-assessed, investigators, patient and parents found significant improvement of SVMs during the sirolimus period. Considering pain, relative changes showed significantly decrease from the observational to the interventional periods for LMs (2.5 ± 3.1 at M0 to 3.6 ± 3.4 at MS and 1.3 ± 2.1 at M12, p=0.005) but were not for VeMs. Quality of life significantly increased under treatment in both groups. During this study, 56 patients experienced 231 AEs during sirolimus period, and 28 patients had 54 AEs during the observational period. Among the 231 AEs, 89 were probably linked to sirolimus (no serious AEs), and 106 were possibly related to sirolimus, among which 5 AEs were considered serious. There was no life-threatening AE.

Conclusion – Sirolimus seems an efficient treatment for painful symptoms linked to SVMs for children aged > 6 years, especially to SVMs with a lymphatic component. At this age, efficacy in reducing the SVM volume is however limited. Investigations should be performed

to assess whether sirolimus at very early ages of life would be helpful for preventing increase in SVMs volume with lymphatic component. Long term data on safety are also required, as well as data on how long treatment has to be maintained.