**A pilot study in patients with congenital low-flow vascular malformation treated with low dose sirolimus**

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*Supplemental Table S2: Supplemental Table S1: Details of the pilot study, part 2.*

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|  | **Dechallenge phase** | **Rechallenge** | | | | **Overall results** | |
| **Pt No** | **Duration of return of pain/symptoms** | **Duration of sirolimus intake** | **Symptoms before restart of sirolimus; reason for restart** | **Symptoms after restart of sirolimus** | **Vascular malformation size, as assessed using MRI** | **Related adverse events (grade;relation to sirolimus)** | **Overall therapeutic response** |
| 1 | 7 weeks | 36 months | Return of severe pain, increase in volume of low-flow vascular malformation | Pain reduction, reduction in volume. Physical exam: no blue coloring of low-flow vascular malformation | No change after six months. Possible slight decrease of cysts on plantar side of feet, slight volume decrease in low-flow vascular malformation after one year of sirolimus use. No change after 17 months compared with one year of sirolimus use | Flu (1;3), aphthous stomatitis (1;4), eczema ankles (1;2), upper airway infection (1;3), abdominal ache (1;2), throat ache (1;2), menorrhagia (2;3), tiredness (1;2), and urinary tract infection (2; 3) | Pain free during sirolimus use |
| 2 | 4 weeks | Ongoing | After a stop of four weeks, new lesion found on right knee, tiredness, leakage of lymph, return of pain, impaired QoL. | No leakage after two weeks, pain reduction and improvement of condition | Reduction of cysts in proximal lower extremity of low-flow vascular malformation | Temporary tiredness (1;2), flu (1;3), viral infection (2;2), and viral infection (2;3) | Pain free during sirolimus use, improvement of QoL |
| 3 | 2.5 months | 23 months | Pain epigastric cyst, increasing volume of lower extremity in low-flow vascular malformation | Reduction of frequency of leakage | No change | Common cold (1;2), erythema with pustules on face (1;4), aphthous stomatitis (1;4), flu (1;3), gastritis (1;2), menorrhagia (1;3), amenorrhea (1;3), headache (1;3), and chest pain (myalgia) (1;2) | Reduction of complaints but not completely free of pain |
| 4 | 25 days | 10 months | Prevention of progression of cysts, no change in other cysts (vertebral) | See the results of MRI | During Rechallenge phase: progression of cysts in spleen and cyst on retroperitoneal left side, no change in vertebral cysts (e.g., C4, Th 4, and Th 10),increase in cysts in spleen. End of Rechallenge phase: progression in volume and amount of cysts in spleen, progression in volume of retroperitoneal and right side para-iliac cyst and cyst on supraclavicular left side, no change in vertebral cysts (e.g., C4), increase in cysts in spleen | Aphthous stomatitis (1;4), infected cyst (3;2), leucopenia (1;2), elevated liver enzymes (1;3), papulopustular rash (1;3), headache (1;3), general malaise (1;2), and common cold (1;2) | No remission |
| 5 | 15 days | Ongoing | Severe pain, increase of circumference of lower extremity during stop | Pain free after 2.5 weeks Sirolimus | MRI before Rechallenge showed a minimal reduction compared with the MRI after six months of sirolimus use. MRI after Rechallenge: no further reduction compared with previous MRI | Upper airway infection (1;3), obstipation (2;2), viral infection (1;2), amenorrhea (1;4), dysmenorrhea (1;4), neutropenia (2;3), tinea pedis (1;2), Epstein-Barr-virus infection (1;2), influenza virus infection (1;2), general malaise (1;2), tiredness (1;2), laryngitis subglottica (1;3), naevus naevocellularis excision (2;2), papulopustular rash (1;3), and infection in vascular malformation (2;2). | Pain free during sirolimus use, partial resection possible after sirolimus use |
| 6 | Not restarted because of loss of energy during sirolimus treatment | Not restarted | Erection dysfunctionality, urinary problems | Not restarted | Not restarted | Common cold (1;3), obstipation (1; 3), diarrhea (1;2), liver enzyme elevation: ALT (2;4), and AST (1;4). | Reduction of complaints but not complete free of symptoms, no radiologic improvement |
| 7 | 10 days | Restarted with mTOR inhibitor | Return of vesicles after 10 days | Restarted with mTOR inhibitor | No MRI | Increase of frequency of epileptic insults (2;2), gastro-enteritis (1;2), and erysipelas (2;2) | Partial remission: less pain, fewer infections |
| 8 | 2 months | 8 months | After two months, return of pain symptoms | Pain reduction, no pain medication needed, stopped after three months of sirolimus use, pain free for six weeks, after which pain returned | No MRI | Headache (1;2), rhinosinusitis (1;3), tiredness (1;3), reduced appetite (1;3), joint pain (1;3), muscle ache (1;2), decrease serum phosphate (2;3), borderline hypertension (1;3), infection related lymphoma (1;3), urinary tract infection (1;3) | Pain free during sirolimus use |
| 9 | 3 weeks | Ongoing | Severe pain, increased circumference during walk | Partial response: reduction of lower extremity circumference, pain reduction | No change | Aphthous stomatitis (2;4), verrucae plantaris (2;2), hypophosphate (1;2), gastro-enteritis (1;3), fever (1;3), prolonged wound healing (1;3), ear infection (2;3), upper airway infection (1;3), neutropenia (2;3), prurigo after sun caused eruption (1;2), and flu (1;3) | Pain reduction |
| 10 | 6 weeks | Ongoing | Increase of tongue volume, noduli and nodus tongue | Tongue in submandibular position | After Rechallenge: overall further substantial reduction of vascular malformation size | Aphthous stomatitis (1;4), upper airway infection (1;3), generalized malaise (1;3), fever (viral infection) (1;3), gastro-enteritis (1;3), fever (1;3), tonsillitis (1;3), tired (1;2), cough (1, 3), and flu (1,2) | Decrease of volume of low-flow vascular malformation in the neck, tongue. and submandibular; partial submandibular resection was possible. Further size reduction following submandibular bleomycin sclerosis, decannulation, and tongue bleomycin sclerosis because of increased tongue volume |
| 11 | 4 months | Stopped after four months of sirolimus use due to inefficacy | Within one week, pain returned | No further pain reduction | No MRI | Common cold (1;3) and elevation of triglycerides (2;3) | Pain only reduced during Challenge phase, not Rechallenge phase |
| 12 | Not restarted | Not restarted | Not restarted for logistical reasons | Not restarted | Not restarted | Aphthous stomatitis (1;4), prostatitis (2;3), and upper airway infection (1;3) | Pain free during sirolimus use |

*Continuing phases: outcomes of the pilot study for 12 patients treated with sirolimus at Radboud university medical center, Nijmegen, the Netherlands. Pt: patient. Grade 1–4, Relation to sirolimus use 1–6 (1: unrelated, 2: unlikely, 3: possibly, 4: probably, 5: definitely, 6: no info available).*