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# Tacrolimus in Gastrointestinal Bleeding in a Young Boy With Hereditary Hemorrhagic Telangiectasia

*Jessica M. Pruijsen, MD, †Steven Kroon, MD, †Johannes J. Mager, MD, PHD, ‡Laura B. Bungener, MD, PHD, and *Hubert P. J. van der Doef, MD, PHD

**Abstract:** Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease in which gastrointestinal bleeding is a rare presenting symptom in children. Gastrointestinal bleeding in children is treated locally by endoscopy. When a focus of bleeding cannot be reached by endoscopy, management of these patients can be challenging. Previous reports showed a favorable outcome of treatment with tacrolimus in an adult HHT patient with liver vascular malformations and epistaxis and in a HHT patient with pulmonary hypertension. We report the first pediatric HHT patient who benefited from tacrolimus treatment. Our case demonstrated a remarkable decline in blood transfusions and better quality of life during the period of tacrolimus treatment.

**Key Words:** Rendu Osler, Rendu Osler Weber, treatment

## INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease characterized with epistaxis, arteriovenous malformations and mucocutaneous telangiectases. Gastrointestinal (GI) bleeding is a rare presenting symptom in children. Bleeding is treated symptomatically, but can be difficult to control. GI bleeding in children is treated locally by endoscopy. When a focus of bleeding cannot be reached by endoscopy, management of these patients can be challenging. Previous reports showed a favorable outcome of treatment with tacrolimus in an adult HHT patient with liver vascular malformations and epistaxis and in an adult HHT patient with pulmonary arterial hypertension (1,2). We describe the first pediatric HHT patient treated with tacrolimus with good clinical response on GI bleeding.

## CASE REPORT

An 8-month-old boy was referred to our tertiary pediatric gastroenterology department because of melena, iron deficiency anemia (hemoglobin level of 3.8 mmol/L, MCV67 fl, ferritin 2.7 µg/L) and a family history of HHT (father of mother and brother of mother diagnosed with HHT). Physical examination showed no substantial abnormalities. As GI bleeding at this age is a very rare manifestation of HHT additional investigations (Meckelscan, gastroduodenoscopy, ultrasound, and computer tomography) were performed to search for the origin of melena, but were negative. After invasive angiography, which showed teleangiectases in jejunal branches of the superior mesenteric artery with normal aspect of the branches of the celiac trunk, HHT was suspected. Genetic investigation confirmed the diagnosis HHT type 1 [heterozygote mutation *ENG* c.247G>T; p.(Gln83*)] in the boy and his mother.

The boy frequently needed blood transfusions and had behavior problems and poor quality of life due to abdominal pain, fatigue and frequent hospital visits (Fig. 1). Unfortunately, it was not possible to treat the GI bleeding by endoscopy. Tacrolimus was started as previous reports showed favorable outcome in HHT adult patients and after discussion in the European Reference Network on Rare Multisystemic Vascular Diseases (VASCERN).

Tacrolimus was started at the age of 2.5 years (target trough levels of 2–4 µg/L), which was used in the next 14 months. In these months, the GI bleeding persisted but decreased in frequency. In this phase, he did not require any blood transfusion, but 3 iron infusions were given (Fig. 1). During tacrolimus therapy, he suffered frequently from epistaxis which disappeared after coagulation by an Ear Nose and Throat doctor. He felt much better; abdominal pain, fatigue, and behavioral problems decreased significantly. Adverse effects of tacrolimus were mild recurrent ear infections, responding to standard therapy.

Due to a unilateral viral parotitis, we stopped the tacrolimus after 14 months of therapy and we had the opportunity to explore the clinical course without tacrolimus. In the next 2 months without tacrolimus, the GI bleeding increased for which he had 1 iron transfusion and 3 blood transfusions (Fig. 1). In this period abdominal pain, fatigue and behavioral problems increased and were comparable with the period before the start of tacrolimus. There were no signs of nose bleeding and he had normal oxygen saturation and normal breathing. After restart of the tacrolimus, quality of life improved again with decrease of abdominal complaints. During the follow-up of 9 months since the restart of tacrolimus, 1 iron and 3 blood transfusions were required.

Parents have given their permission to publish this case report about their son.

## DISCUSSION

We report the first pediatric HHT patient who benefited from tacrolimus. Our case demonstrated a remarkable clinical improvement in blood transfusions and better quality of life during the period of tacrolimus treatment. Mean interval between blood transfusions was 65 days in the 2 periods with tacrolimus and 34.5 days without tacrolimus. In adult HHT patients, 2 cases with tacrolimus treatment are reported. In both patients, epistaxis and/or GI bleeding was improved with a decrease in the number of required blood transfusions (2,3).

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From the *Pediatric Gastroenterology and Hepatology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; †Department of Pulmonology, St. Antonius Hospital Nieuwegein, The Netherlands; and ‡Department of Laboratory Medicine, Transplantation Immunology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

The authors report no conflicts of interest.

Parents are aware of this case report and gave permission.

Correspondence: Jessica M. Pruijsen, MD, Department of Pediatric Gastroenterology and Hepatology, University of Groningen, University of Groningen, University Medical Center Groningen, Hanzeplein 1, PO Box 30 001, 9700 RB Groningen, The Netherlands. E-mail: j.m.pruijsen@umcg.nl



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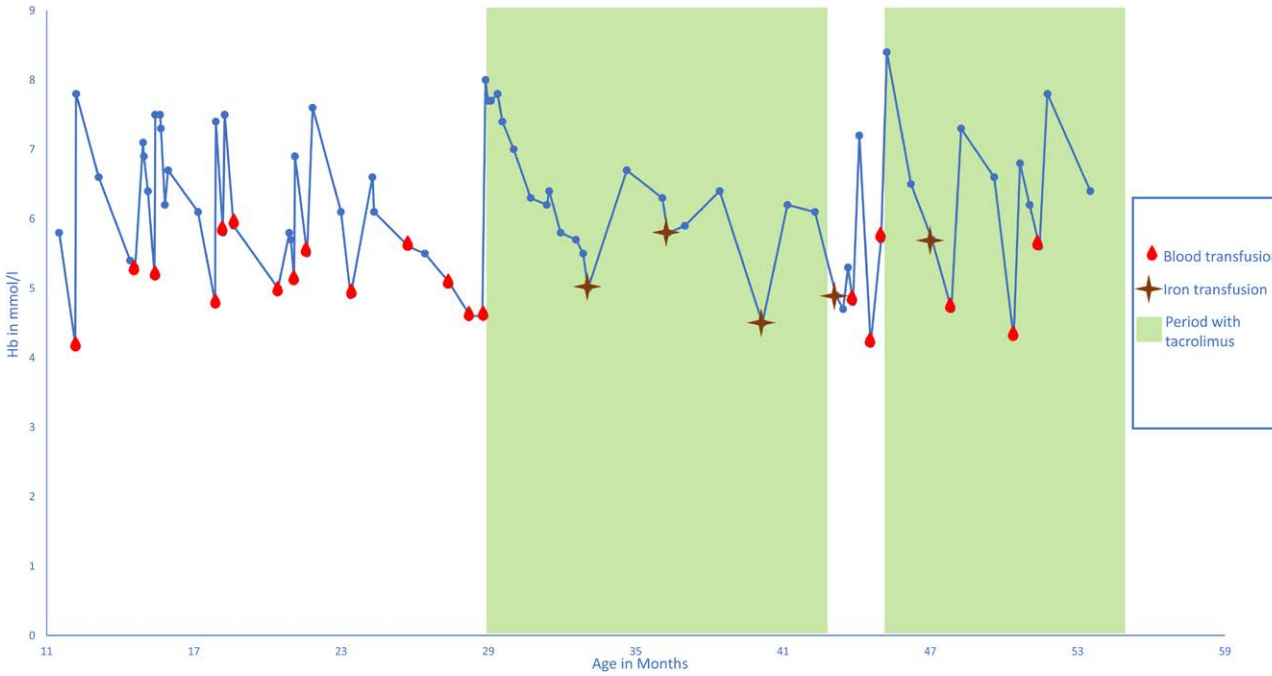


**FIGURE 1.** Tacrolimus use in relation to blood transfusion rate; Hemoglobin level (Hb) in mmol/l is pointed out in time (in months of age of boy). Number of blooftransfusions (🩸) and ironinfusion (✦) are shown. The shaded areas are the periods in which tacrolimus was described.

In the literature, the benefit from immunosuppressive drugs in pediatric patients with vascular diseases is described. In 2011, a case of a 12–year-old girl with blue rubber bleb syndrome and sirolimus was reported (4). After the start with sirolimus, a significant reduction of the vascular masses and no GI bleeding occurred. In a period of withdrawal, GI bleeding reoccurred and disappeared after starting sirolimus again. Although sirolimus and tacrolimus have a different metabolic pathway, respectively, mammalian target of rapamycin (mTOR) and calcineurin inhibition, both have an effect on the angiogenesis.

In HHT, 80%–90% of the cases are caused by mutations in activin receptor-like kinase 1 (*ACVLR1*) and endoglin (*ENG*). These genes are encoding for bone morphogenetic protein (BMP) receptor, activin receptor-like kinase 1 (ALK1), and co-receptor endoglin, respectively (1). Due to ALK1-endoglin receptor activation by BMP 9 and 10, eventually Smad 1/5/8 complexes are formed, which control specific gene expression programs in the nucleus. The exact pathogenesis of HHT is yet unknown, but studies have shown that reduction of Smad 1/5/8 and overactivity in vascular endothelial growth factor (VEGF) and VEGF receptor 2 (VEGFR2) signaling play a key role in the process of vascular disbalance. Therapy is targeted for these different signaling pathways. Studies in endothelial cells and in mice show that both tacrolimus and sirolimus lead to an increase of the Smad 1/5/8 signaling pathway (5,6). Tacrolimus increases the upregulation of ALK1 and ENG receptors (1) and, in addition, has a potential benefit on inhibition of VEGF signaling (5). To inhibit multiple signaling pathways dually, the combination of nintedanib, which is a VEGFR2-targeting receptor tyrosine kinase inhibitor, and sirolimus, an mTOR inhibitor has shown to be potential beneficial. In a specific BMP 9/10-immunoblocked (BMP 9/10ib) neonatal mouse model of HHT, combination of these drugs prevented vascular pathology in oral mucosa, lungs, and liver with significant less GI bleeding and anemia. Besides blocking the overactivation of mTOR and VEGFR2 at the same time led to more activated Smad 1/5/8 signaling, which demonstrated that these pathways play a key role in HHT pathogenesis (7).

According to the latest international guidelines, published after our case was presented, another targeted therapy for GI bleeding is the anti-VEGF blocking drug Bevacizumab (8). We did not consider to start with Bevacizumab in our patient, as we already experienced positive effects of tacrolimus. Bevacizumab is only reported in one pediatric patient and severe side effects have been reported (malignant hypertension, severe proteinuria, lymphopenia and (GI-)bleeding) (9,10).

In conclusion, we describe the first pediatric HHT patient who benefited from tacrolimus treatment. During tacrolimus treatment, the patient had decreased GI bleeding and a decreased need for blood or iron transfusions. Our finding supports the potential benefit of tacrolimus in difficult to treat pediatric vascular disease patient, like in HHT.

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