Pharmacological Treatment of a Diffuse Arteriovenous Malformation of the Upper Extremity in a Child

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Abstract: A young girl with an arteriovenous malformation involving the right upper extremity developed rapidly progressive bony destruction that did not respond to embolization. Treatment with marimastat, starting at 3 years of age, resulted in rapid resolution of pain and gradual healing of bony destruction, associated with regression of the intraosseous arteriovenous shunts. New arteriovenous shunts with bony destruction developed over the years and responded to an increase in the dose of marimastat. Interruption of therapy resulted in recurrence of pain and formation of new lesions. The patient has been treated in this way for 12 years with no adverse effects from the drug.

Key Words: Arteriovenous malformation, embolization, angiogenesis, matrix metalloproteinase inhibitor, marimastat

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Arteriovenous malformation (AVM) is characterized by arteriovenous shunting resulting in progressive vascular dilation, venous hypertension, destruction of tissue, and, rarely, cardiac decompensation due to a high output state.[1–3] Cure is difficult or impossible to achieve; for AVM of a limb, amputation is often necessary to relieve symptoms. Until recently, the ineffectiveness and toxicity of the pharmacological alternatives precluded their use for these otherwise benign vascular lesions. Novel therapeutic targets for the treatment of angiogenesis-dependent conditions have been revealed by advances in molecular biology and genetic basis of these disorders. As described over the last decade, angiogenesis is a highly invasive process that requires proteolysis of extracellular matrix (ECM), proliferation and migration of endothelial cells (ECs), as well as synthesis of new matrix components.[4,5] Expansion or progression of vascular malformations has been attributed to the production of matrix metalloproteinases (MMPs), a family of zinc-dependent proteinases involved in the turnover of a variety of ECM components.[5–9] To summarize this process, the initiating proangiogenic stimulus results in the formation of a migrating solid column of ECs called the *vascular sprout*. Proteolytic activity is presumably focused into the advancing front of the column to create a defect in the ECM through which ECs migrate. Behind this advancing front of protease activity, a region of differentiation develops in which the ECs tightly adhere to one another, form a new basement membrane, stop proliferating, and develop a lumen. This process is tightly controlled in both temporal and spatial fashion and is part of normal tissue remodeling during wound healing, embryogenesis, or menstrual cycle. It can be grossly abnormal as a result of somatic mutations resulting in an increased level of a particular MMP.

We hypothesized that abnormal MMP activity contributed to the progression of an AVM in a child who did not respond to endovascular treatment and that giving a MMP inhibitor might reverse the process. We report the first successful pharmacological control of the symptoms and evolution of a diffuse AVM. We discuss the rationale for using marimastat and elaborate on the proposed mechanism for its action in this setting.

CLINICAL REPORT

A term female neonate was noted to have a capillary stain involving the right upper extremity and shoulder. By 8 months of age, the arm had enlarged and was painful on supination. Radiography showed expansile and lytic abnormalities in the radius, ulna, and humerus. Magnetic resonance imaging revealed corresponding fast-flow vascular lesions, predominately intraosseous and subperiosteal in location. Pathological fracture of the right humerus occurred at 10 months and again at 12 months of age. After evaluation by pediatric specialists in orthopedic, vascular, and plastic surgery, no operative treatment, except for amputation, was deemed feasible. She underwent angiography and embolization at 12 months of age. Angiography confirmed AVM involving the humerus, radius, and ulna, as well as the adjacent soft tissues. Between May 1994 and July 1996, she underwent 16 endovascular procedures, involving transarterial and direct percutaneous embolization of the AVM using opacified *n*-butyl-2-cyanoacrylate (NBCA) and absolute ethanol. She developed progressive enlargement of the index and small fingers (Fig. 1). Plain radiographs showed new lytic osseous lesions with no evidence of reossification in the areas that had been embolized. In the spring of 1996, she complained of increasing pain and progressive enlargement of her index finger. Symptoms included waking at night with pain, irritability, pulling at her shoulder, difficulty dressing, and disuse of the right hand. She was unable to flex the index and small fingers or fully extend the small finger. She held the right hand next to her body and used the left hand for most activities and required ibuprofen daily for analgesia.

In March 1996, the patient was presented to a multidisciplinary panel at the weekly meeting of the Vascular Anomalies Center. The consensus was that the AVM was expanding despite multiple embolizations. She was evaluated for possible treatment with angiogenesis inhibitors. Serum vascular endothelial growth factor (VEGF) level was 492 pg/mL, considered minimally elevated

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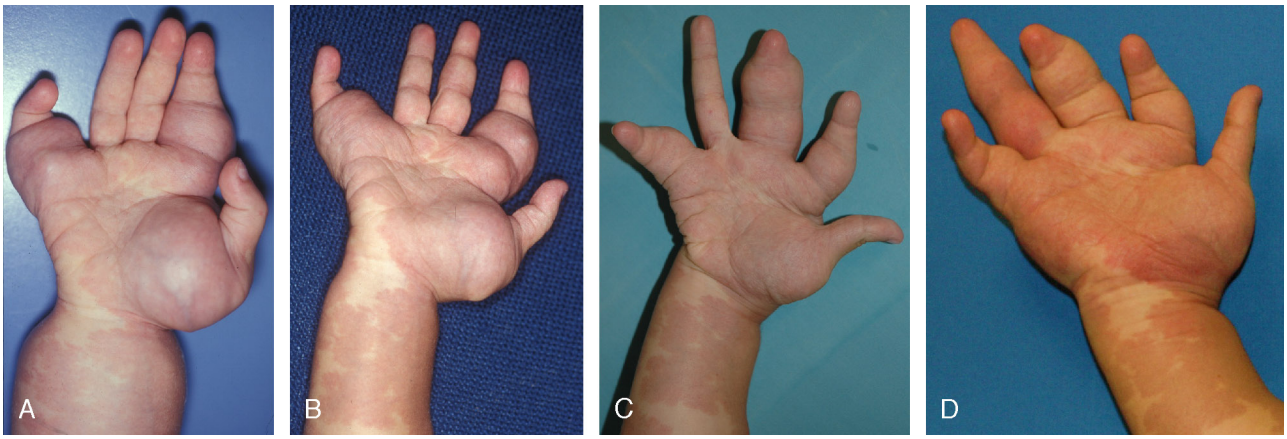

FIGURE 1. Clinical photographs of the right hand from 1996 to 2006. A, August 1996, at 3 years of age, before starting marimastat therapy. The wrist, base of thumb, index finger, and small finger are swollen. B, October 1999, after receiving marimastat for 3 years, there has been dramatic improvement in the swelling of the wrist, thenar eminence, and small finger. C, In 2004, the photograph shows further decrease in the soft swelling of the thenar eminence, index finger, and small finger, while the middle finger has expanded. D, December 2006, the middle finger is less swollen, but there are swelling and increased length of the ring finger.

(normal adult serum VEGF is 18–398 pg/mL). Because of the prominence of osteolysis, increased metalloproteinase activity was suspected, but not confirmed. Permission was requested from the Food and Drug Administration and institutional review board, as well as the pharmaceutical manufacturer, British Biotech (Oxford, UK), for a therapeutic trial with marimastat, a broad-spectrum metalloproteinase inhibitor. Approval, including a single patient investigational new drug, and informed consent were obtained, and pharmacological therapy began on July 25, 1996. She received 30 mg of marimastat daily. Her parents kept a daily log of pain and analgesic requirement and measured (weekly for 2 months, then monthly) the circumference of her hand, wrist, forearm, and elbow. Radiographs of the hand, forearm, and humerus were obtained every 2 months for the first year and then approximately 3 times per year. After 8 weeks of marimastat therapy, she no longer required analgesia.

In January 1997, marimastat was discontinued for 8 days because she had an upper respiratory tract infection. Six days later, she again began to complain of pain, and this promptly resolved after resuming marimastat. In February 1997, she fractured the right humerus during a fall on her arm. By August 1997, at 4 years of age, there was improved flexion of her index and small fingers, and radiographs showed healing of the lytic lesions in the humerus, radius, and ulna, although the expansile lesions of the proximal phalanges of the index and small fingers had enlarged. In February 1999, following a series of upper respiratory infections, marimastat was discontinued for 8 weeks, and again, she complained of pain in the carpal region and required analgesics. Her symptoms subsided gradually after recommencing treatment. A radiograph taken in March 1999 showed some new lytic changes in the middle phalanx of the middle finger, and in October 1999, she developed swelling and increased pulsatility in that digit. She underwent

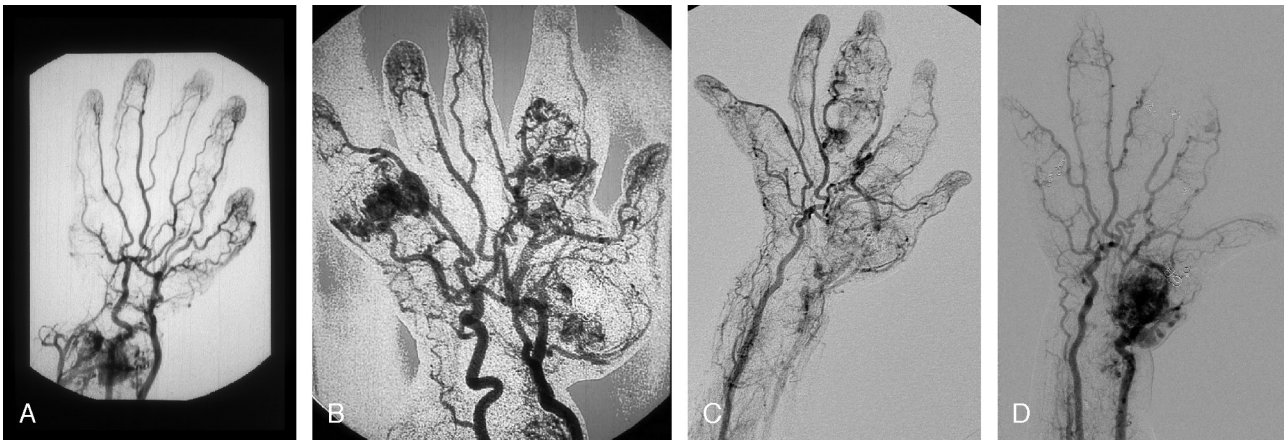

FIGURE 2. Serial angiograms of the right hand. The images have been edited to correspond to the orientation of the clinical photographs. A, May, 2004. The initial angiogram shows focal intraosseous arteriovenous shunts in the distal radius and ulna, but none in the hand. B, In 1998, there are direct arteriovenous shunts in the proximal phalanges of the index and small fingers and in the thenar eminence and first metacarpal. C, In 2002, angiography shows obliteration of the focal shunts in the index and small fingers, as well as the thenar eminence. New lesions are seen in the middle finger. D, In 2007, there are new AVMs in the carpus and index fingers.

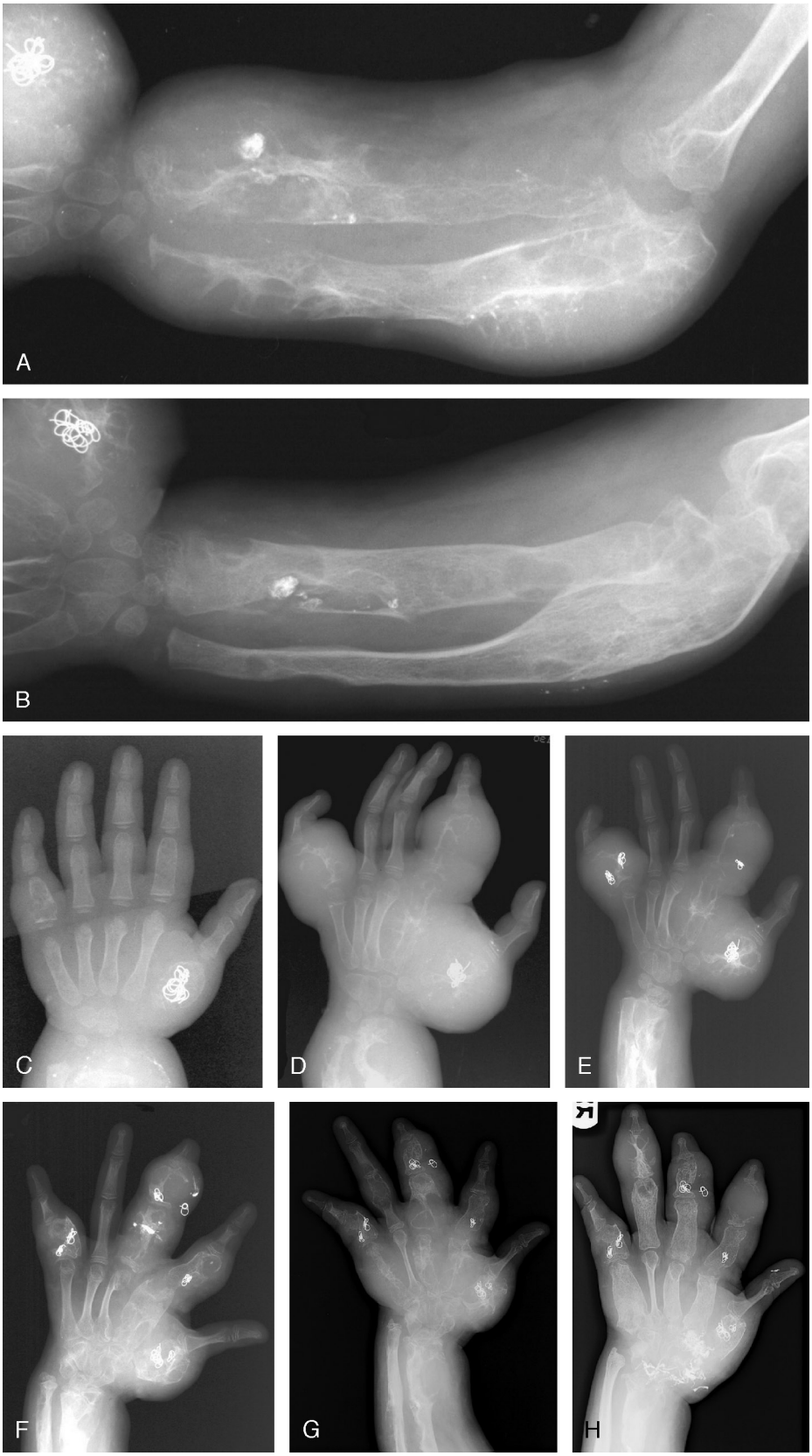

FIGURE 3. Serial radiographs of the patient's forearm and hand. Marimastat was started in July 1996. The metallic coils were introduced percutaneously into the varices draining the focal shunts. The images have been edited to correspond to the orientation of the clinical photographs. A, Radiograph of the radius and ulna in July 1996, immediately before starting marimastat, shows severe bony destructive changes and soft tissue swelling. Radiopacities represent residual opacified NBCA, most of which had been resorbed. B, Radiograph of the radius and ulna in 1998, after 2 years of marimastat, shows definite evidence of bone healing and remodeling. C–H, Radiographs of the right hand in 1995 (C), 1996 (D), 1998 (E), 2002 (F), 2006 (G), and 2008 (H). The final radiograph (H) shows healing of most of the lytic defects, but a new one has formed in the distal phalanx of the index finger.

4 embolizations between February and November 2000, to treat the new arteriovenous fistulae in the middle phalanx of the third ray. Serial angiography during these procedures showed gradual improvement in the intraosseous AVM, including those areas not recently embolized (Fig. 2). By November 2, 2000, direct intraosseous arteriovenous shunting was no longer present by color Doppler ultrasonography. Clinical assessment in October 2000 showed improvement of all parameters with excellent function of the right upper extremity, except for limited supination of the elbow. She was able to flex and extend all of her digits and had improved strength in the right upper extremity. Her marimastat dose was increased gradually as she grew. She developed new shunts in the phalanges of the middle finger in 2001 and underwent additional endovascular treatment. Between 2002 and 2005, the AVM was stable and did not require intervention. In 2006, at the time her menstrual cycles began, she began to experience more swelling and pain, and evaluation revealed AVM in the ring finger. This worsened over a period of 6 months, during which the dose of marimastat was increased gradually, and pain diminished. In 2007, she developed severe swelling of her wrist and index finger, and radiographs showed expansion and destruction of the metacarpal and carpal bones and enlargement of a lytic defect in the distal radius. Doxycycline, 100 mg daily, was added, and marimastat was increased to 120 mg daily in 2 doses. Radiographic follow-up showed gradual healing of the bones of the ring finger and the metacarpal bones, but the swelling at the wrist worsened, and ultrasonographic evaluation demonstrated a large AVM underlying the swelling. Angiography and embolization were carried out. Aside from the large shunt at the wrist, and a focal intraosseous shunt in the distal phalanx of the index finger, the angiogram showed a stable appearance, with no focal shunts in the arm or forearm.

The serial measurements taken after initiation of marimastat showed progressive decrease in the circumference of the wrist, forearm, and elbow during the first 5 years and then gradual increase that was proportional to her growth in height and weight. The circumference of the hand, index finger, and small finger increased, corresponding to the development of new lesions, and then decreased. Radiographs showed gradual healing of the osseous lesions of the humerus, radius, and ulna up until March 1999, after the 8-week interruption in marimastat treatment, when there was some worsening of the lytic lesions throughout the right upper extremity (Fig. 3). Subsequent radiographs showed improvement in all bony lesions, except for the middle finger. During episodes of somatic growth, she intermittently developed recurrence of pain and swelling, and radiographs showed new areas of bony destruction and soft tissue swelling. Some of the bones in her hand were severely disrupted, but over time, healing and remodeling occurred in each affected site. She developed bowing of the radius and ulna and a Madelung deformity of the wrist. Her right hand and fingers were significantly larger than the left hand, and the overgrowth affected some digits more than others. By 2008, the strength in her hand and wrist was poor.

During the 12 years of treatment, the patient showed normal somatic and psychological growth and development and normal blood cell counts and routine chemistry values, and she demonstrated no side effects from the drug.

DISCUSSION

In 1964 and 1965, Malan and Puglionisi[10,11] published 2 review articles in which they accurately described the natural history and clinical, histological, and angiographic findings of fast-flow vascular anomalies in the extremities. Several subsequent series have emphasized the progressive clinical course and difficulties in treatment of these anomalies.[2,3,12,13] Most patients had recurrence after attempted resection or embolization, and many required amputation for severe pain, nonhealing ulcers, and/or congestive heart failure.

Arteriovenous malformation originates from defective embryonic vasculogenesis and angiogenesis resulting in abnormal communications between arteries and veins that bypass the high-resistance capillary bed. The abnormal channels connecting the arteries and veins constitute the "nidus." Arteriovenous malformation of the extremity is usually diffuse, including macroscopic arteriovenous fistulae as well as diffuse permeative microshunts. The lesions evolve, worsening with advancing age. Genetic abnormalities have been identified in some patients with inheritable AVM, including hereditary hemorrhagic telangiectasia, capillary malformation–AVM, and PTEN-related AVM.[14,15] Hereditary hemorrhagic telangiectasia is caused by loss-of-function mutations in the genes encoding endoglin and ALK1 and receptors for type III and type I transforming growth factor β that are exclusively expressed on the vascular EC surface.[16–18] Mice lacking these genes develop arteriovenous communications, characterized by deficient smooth muscle differentiation and recruitment, and arrested EC remodeling.[19,20] Recently, RASA1 mutations have been identified in families with AVM and cutaneous capillary malformations.[21–23] PTEN mutations cause AVM in addition to mesenchymal "hamartomatous" masses and other soft-tissue tumors.[24–30] These mutations may result in either up-regulation of proangiogenic proteins or in the suppression of endogenous inhibitors of angiogenesis. Studies of angiogenic proteins have shown up-regulation of VEGF and basic fibroblast growth factor in and adjacent to human brain and dural AVM; it has been suggested that these factors may be responsible for recurrence after treatment.[31] Endothelial cells isolated from peripheral AVM show elevated proliferation in culture and lack of inhibition by cytokine stimulation, suggesting that these ECs have defective regulation of proliferation because of reduced apoptosis.[32] Nevertheless, elevated circulating growth factors have not been detected in patients with large peripheral AVM.[33] This finding suggests that angiogenesis inhibitors would not be effective in the primary treatment of AVM.

It is likely that genetic alterations disturb the tenuous balance of normal tissue remodeling that is normally controlled by strict spatial and temporal expression of a wide variety of molecules such as growth factors, adhesion molecules, ECM proteins, and MMPs. The meticulous control over the levels and time and place of growth factor expression has been suggested by in vitro studies. For example, the treatment of ECs with exogenous MMP-2 induced dose-dependent morphological changes consistent initially with an angiogenic response (tube formation) but, after a plateau, in a reversal of capillary tube formation.[34] Similarly, in a monolayer culture of ECs, constitutional levels of pro–MMP-2 with little activation of this protease were detected, whereas in three-dimensional collagen gels, the pro–MMP-2 transcript was clearly up-regulated.[35] Many of the events involved in EC invasion are dependent on the ECM that composes the abnormal, genetically modified lesion stroma. The elimination of stromal influences is difficult with presently available endovascular techniques or partial surgical resection.

Transfemoral embolization involves supraselective catheterization of feeding arteries, usually with microcatheters and injection of occlusive material.[36–44] Most embolic techniques occlude the feeding arteries, and do not destroy the "nidus." After initial enthusiasm, it became clear that standard arterial embolization usually is followed by recurrence and often worsens tissue ischemia.[3,5] Direct injection of ablative materials, such as NBCA or ethanol into the nidus or the venous side of the AVM, seems to give better results.[39,45–47] However, embolization with ablative liquid material is a difficult technique that can be associated with a

high rate of complications including tissue necrosis, neuropathy, and systemic and cardiovascular complications.[47] Supraselective arterial embolization and direct intralesional injection with NBCA and ethanol were used aggressively in this patient. Although excellent technical results were achieved, as judged by postembolization angiographic improvement and initial regression of clinical signs, the lesions recanalized, and new areas of bony destruction were evident at each follow-up visit during the course of endovascular treatment.

The blood flow disturbance caused by residual AVM continues to modify the endothelial cellular environment. Recent findings suggest that changes in cell shape (such as the mechanical forces resulting from residual AV fistulas) alter the transcription of MMPs[48] and initiate enhanced MMP production on different ECM substrates.

Marimastat is a broad-spectrum MMP inhibitor that can be administered orally and has 50% inhibitory concentrations in the nanomolar range for collagenases, gelatinases, matrilysin, and stromelysin.[49] It was chosen for this patient in 1996 because the osteolysis associated with the expansion of her AVM was believed to be, at least in part, caused by the increased activity of metalloproteinases. Metalloproteinases are composed of a growing family of proteolytic enzymes that are classified into 4 groups based on their protein domain structures.[50] The smallest subgroup consists of matrilysin (MMP-7); the second one comprises collagenases (MMP-1, MMP-8, and MMP-13), stromelysins (MMP-3, MMP-10, and MMP-11), and metalloelastase (MMP-12). The third group contains 2 gelatinases (MMP-2 and MMP-9), and the fourth consists of membrane-type MMPs (MT-MMPs: MMP-14 or MT1-MMP, MMP-15, MMP-16, and MMP-17). This vast array of tissue-specific enzymes is normally controlled by tissue-specific tissue inhibitors of metalloproteinases, which are generally able to inhibit the active forms of MMPs in a timely fashion. Abnormal levels of MMPs have been documented in certain cancers,[5] in brain AVM tissue,[7,8,51] and in experimental AVM in animals.[9] Urinary metalloproteinases are detectable in patients with extensive AVM.[52] In animal models, inhibitors of MMP have been shown to prevent arterial enlargement that occurs with surgically made arteriovenous fistulas.[53] Unfortunately, clinical trials using marimastat in cancer treatment have been disappointing, because of a high rate of musculoskeletal side effects in adult patients.[54] Our patient had a convincing response to marimastat. The serial circumferential measurements of the forearm decreased during the first 7 years of drug therapy. Her pain, which was severe enough to limit the use of the affected limb, decreased over the first 8 weeks of treatment so that she no longer complained of pain or required analgesics. Regression of soft tissue swelling and radiographic evidence of healing of osseous erosions and bony remodeling followed. During periods when the medication was stopped because of acute systemic illness, her pain recurred, and subsequent radiographs showed some worsening of the lytic changes of the bones. When marimastat was resumed, her pain promptly abated, fulfilling one of Koch's postulates. During the 12 years of pharmacological treatment, recurrence of symptoms and appearance of new bony destruction seemed to coincide with periods of somatic growth. Improvement in pain and swelling has generally been observed within a few weeks of increasing the dose of medication.

In conclusion, the positive effect of marimastat in this child supports our hypothesis that MMPs play a role in the evolution of AVM and that their down-regulation can result in sustained therapeutic response. Furthermore, inhibition of metalloproteinase activity may be effective in controlling the destructive effects and symptoms in AVM of bone. It is unclear whether the positive therapeutic response in this child was idiosyncratic in origin or whether our rationale may represent a genuine potential for future therapy. Further investigation into the underlying mechanisms of MMP activity in AVMs, as well as other untreatable vascular lesions, is warranted.

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