

Mycophenolate Mofetil for the Treatment of Takayasu Arteritis: Report of Three Cases

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Background: Takayasu arteritis is a rare form of chronic inflammatory disease of the large arterial vessels. Some patients do not respond to steroids or immunosuppressant drugs.

Objective: To evaluate the effect of mycophenolate mofetil in patients with severe Takayasu arteritis.

Design: Case series.

Setting: Clinical Research Center for Rare Diseases in Bergamo, Italy.

Patients: Three patients with Takayasu arteritis.

Intervention: Mycophenolate mofetil (2 g/d) given orally in two divided doses.

Measurements: Clinical evaluation and assessment of leukocyte counts were done weekly. Vascular lesions were assessed by using Doppler ultrasonography.

Results: All patients showed clinical benefit, and two resumed work after months of inactivity. Patients were also able to taper and discontinue steroid use. Mycophenolate mofetil was well tolerated, and no signs of toxicity were observed.

Conclusions: Mycophenolate mofetil may be an alternative to steroids and cytotoxic agents in patients with Takayasu arteritis. Before results of controlled trials become available, mycophenolate mofetil should be considered only for patients who do not improve or stabilize with conventional therapy.

Takayasu arteritis is a chronic inflammatory disease that affects large arterial vessels, such as the aorta and its main branches (1). First described in Japan, it is relatively common in Asia (2) but is rare in the western hemisphere (3).

The inflammatory process of Takayasu arteritis causes thickening of the affected vessels. The involved artery narrows, or becomes occluded, causing various symptoms. Inflammatory cell infiltration, which is always found in Takayasu arteritis, suggests that cell-mediated autoimmunity plays an important role in the pathogenesis of the disease (4).

Oral glucocorticoid agents have been used as first-line therapy in Takayasu arteritis and have been reported to limit disease activity and slow disease progression in up to 75% of patients. However, many patients require large maintenance doses of steroids and are at risk for chronic steroid toxicity (5). A remaining 52% of patients require the addition of an immunosuppressive drug, such as cyclophosphamide or methotrexate, but only one third show a positive response (6). Thus, some patients with Takayasu arteritis do not improve, and many have substantial drug toxicity.

We observed three patients with Takayasu arteritis who were dependent on large doses of steroids and had severe signs of steroid toxicity. Despite being treated with corticosteroids and cytotoxic drugs, these patients presented with dramatic manifestations of their disease. We describe how these patients responded to mycophenolate mofetil.

Patients

Three patients with clinical, laboratory, and angiographic data supporting the diagnosis of Takayasu arteritis were treated from February 1997 to April 1998 at the Clinical Research Center for Rare Diseases in Bergamo, Italy. Their medical history is summarized below and in **Table 1**.

Patient 1

In June 1991, a 47-year-old woman experienced sudden onset of malignant hypertension, accompanied by visual disturbances, headache, dizziness, and tinnitus. For 3 years she had nonspecific symptoms, including arthralgias, myalgia, malaise, and leg claudication. Blood pressure at presentation was 240/

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Table 1. Clinical Characteristics of Three Patients with Takayasu Arteritis Treated with Mycophenolate Mofetil

Patient	Age	Duration of Disease	Disease Characteristic at Onset	Characteristic When Mycophenolate Therapy Was Initiated	Steroid Toxicity	Previous Therapy
		y				
1	47	9	Malignant hypertension	Transient ischemic attack	Severe	Glucocorticoids
2	32	7	Upper-limb ischemia	Carotodynia	Very severe	Glucocorticoids, cyclophosphamide, cyclosporine, azathioprine, methotrexate
3	31	3	Upper-limb ischemia	Mesenteric arterial occlusion	Very severe	Glucocorticoids, cyclosporine, methotrexate

125 mm Hg (right arm) and 150/90 mm Hg (left arm); the patient had decreased left radial artery pulse and no artery pulses in the lower limbs. Funduscopy showed hypertensive retinopathy. An angiogram demonstrated occlusion of the left subclavian artery, high-grade stenosis just beyond the origin of the left renal artery, total occlusion of the right renal artery, stenosis of the superior mesenteric artery, irregular narrowing and thickening of the aorta with occlusion of the abdominal segment (after inferior mesenteric artery origin), and a large anomalous collateral artery. She had an elevated erythrocyte sedimentation rate (ESR) (55 mm/h) and a normal serum creatinine level. In November 1991, she began receiving prednisone (1 mg/kg of body weight per day) and antihypertensive medications. Her systemic symptoms resolved, and her ESR returned to normal. To preserve renal function, a prosthetic graft bypass from the lower thoracic aorta to the left renal artery was performed in June 1992.

Steroid therapy was discontinued in October 1992. The patient remained well until August 1996, when she experienced fatigue, transient vertigo, diplopia, and hypomnesia. An angiogram showed occlusion of the right carotid artery in addition to the previous lesions. Prednisone (1 mg/kg per day [65 mg/d]) was given for 2 months and resulted in resolution of systemic symptoms and normalization of ESR. During gradual tapering of the glucocorticoid dose (60 mg every other day), systemic symptoms (malaise, migratory arthralgias, and fatigue) recurred and recurrent cerebral transient ischemic attacks developed; her ESR increased to 40 mm/h. She has never been treated with cyclophosphamide or methotrexate.

Patient 2

A 32-year-old woman presented in April 1990 with weakness, excessive fatigue, fever, weight loss, and general malaise. The patient's ESR was 123 mm/h, her hemoglobin level was 102 g/L, and she had diminished pulses in the upper limbs with upper-extremity blood pressures of 70/40 mm Hg.

An angiogram showed irregularity of the aortic arch and bilateral stenosis of subclavian arteries. She started treatment with three pulses of intravenous methylprednisolone (500 mg/d) followed by oral prednisone (1 mg/kg per day). In April 1991, the disease flared during tapering of the prednisone dose; despite the increase of steroid dosage, the patient never achieved stable clinical remission. Systemic symptoms persisted, the ESR was often elevated, and angiograms showed progression of vascular lesions. Side effects of systemic glucocorticoid administration became marked by June 1995. The addition of cytotoxic agents and plasmapheresis did not induce remission or allow any further reduction in steroid dose. In January 1993, the patient had to stop her work as an office clerk. She became pregnant in March 1997 but had a spontaneous abortion at the sixth week of gestation. When she was referred to us, she was receiving methylprednisolone (16 mg/d) and had cushingoid body habitus, headache, asthenia, carotodynia, and reactive depression; her ESR was 24 mm/h, and her hemoglobin level was 112 g/L. An ultrasonogram demonstrated thickening of the carotid vessels, stenosis of both subclavian arteries, and ectasia of the ascending aorta. Funduscopy showed grade II hypertensive retinopathy.

Patient 3

A 31-year-old woman presented in May 1994 reporting spontaneous pain in her right shoulder and axillary fossa, the Raynaud phenomenon, and rapid muscle fatigue during exercise of the ipsilateral arm. Subsequently, she began to notice general fatigue, fever, and weight loss. She had an elevated ESR, anemia, a right subclavian bruit, and nearly impalpable radial pulses. An angiogram showed narrowing of the bilateral common carotid arteries, obstruction of the right subclavian artery, and stenotic lesions of the left brachial and superior mesenteric arteries. When prednisone (1 mg/kg per day) did not reasonably control her disease, the patient received methotrexate (12.5 mg/wk orally). In October 1996, the patient had constitutional symptoms and

Table 2. Patient Responses to Mycophenolate Mofetil Therapy

Patient	Carotodynia	Transient Ischemic Attack	Systemic Symptoms	Erythrocyte Sedimentation Rate, mm/h	Glucocorticoid Therapy	
					Starting Dosage	Final Dosage
1	—	Resolved in 3 weeks	Absent	20	60 mg on alternate days	Withdrawn
2	Resolved in 4 weeks	—	Absent	20	16 mg/d	8 mg/d
3	—	—	Absent	37	25 mg/d	10 mg/d

an elevated ESR and received six pulses of intravenous cyclophosphamide (800 mg/mo); methotrexate therapy was discontinued. The oral prednisone dose was also increased and then gradually tapered to 25 mg/d. In February 1997, the prednisone dosage was again increased to 1 mg/kg daily and was then tapered slowly. Cyclophosphamide use was discontinued because the patient declined to continue treatment. Upon presentation at our center in June 1996, the patient was receiving prednisone (25 mg/d) but had a high body temperature (39 °C), malaise, and asthenia: The blood hemoglobin level was 101 g/L, and the ESR was 35 mm/h. An angiogram showed stenosis of the celiac artery and a totally occluded superior mesenteric artery in addition to previously demonstrated lesions.

Methods

We sought to determine whether mycophenolate mofetil therapy allows remission of active disease and discontinuation or reduction of steroid use. We explained to the patients why we believed mycophenolate mofetil might control their symptoms better than more conventional treatments. We also informed them that although mycophenolate mofetil had been successfully and safely used in renal transplant recipients, it had never been used in patients with Takayasu arteritis. The Ethical Committee of the Clinical Research Center for Rare Diseases approved the treatment protocol, and patients then gave written informed consent.

Oral mycophenolate mofetil (2 g/d) was given to all three patients in two divided doses. The frequency of side effects seems to be dose related. In a placebo-controlled study, renal transplant recipients receiving 2 g of mycophenolate mofetil per day had substantially fewer adverse effects than those receiving 3 g/d (7).

Patients were evaluated at baseline and after treatment according to the following criteria: 1) presence of vascular inflammation or ischemia; 2) systemic symptoms including fever not attributable to infection, polyarthralgias, and polymyalgias; and 3) elevated ESR. Clinical evaluation and assessment of leukocyte counts were done weekly during the first month of treatment. Thereafter, patients were

seen in the clinic every 2 to 4 weeks. Vascular lesions were qualitatively assessed every 3 months by using Doppler ultrasonography (HDI 5000, Advanced Technology Laboratories, Bothell, Washington).

Results

Clinical Characteristics at Baseline

Baseline clinical characteristics are given in **Table 1**. All three patients had laboratory findings of acute inflammatory disease associated with involvement of the large arterial vessels and target organs with evidence of functional impairment.

Clinical Outcome

Patient responses to mycophenolate mofetil therapy are summarized in **Table 2**.

Patient 1

The patient's systemic symptoms resolved 3 weeks after initiation of therapy, and her ESR decreased to 20 mm/h. After 1 month of mycophenolate mofetil therapy, the prednisone dose could be tapered; 9 months later, prednisone therapy was discontinued. After 15 months of follow-up, the patient remains in stable clinical condition with no instrumental evidence of disease progression. Cerebral transient ischemic attacks never recurred.

Patient 2

Four weeks after initiation of therapy, systemic symptoms and carotodynia resolved. Laboratory markers of inflammation were stable. The steroid dose was halved from the initial dose. An ultrasonogram obtained by Doppler ultrasonography showed no deterioration of the previously described vascular lesions during the 11 months of follow-up. The patient felt so well that she returned to work for the first time in 4 years.

Patient 3

After patient 3 received mycophenolate mofetil for 3 weeks, fever, malaise, and asthenia completely resolved. However, her ESR remained unchanged. At 11 months of follow-up, instrumental assessment

of vascular lesions showed no progression from baseline. The prednisone dosage was tapered to 10 mg/d.

Side Effects

All patients tolerated mycophenolate mofetil without any major toxicity. In particular, leukocyte counts remained within the normal limits, and no patient developed gastrointestinal discomfort.

Discussion

One of the most comprehensive studies of Takayasu arteritis is a report from the National Institutes of Health (6) that describes 60 patients followed for a median of 5.3 years. Sixty percent of these patients achieved reasonable control of the disease with steroids alone, whereas the others required the addition of therapy with cytotoxic agents.

Long-term administration of cyclophosphamide is associated with cystitis, cancer of the bladder, other types of cancer, and infertility (a toxic effect of particular relevance in patients with Takayasu arteritis, who are mostly women of childbearing age) (8). Methotrexate has been proposed as an alternative to cyclophosphamide and has been tested in an open study of 18 patients (5). Although considered less toxic than cyclophosphamide, methotrexate can cause severe bone marrow depression, which in turn may lead to life-threatening infections or spontaneous hemorrhage (9).

Our three patients with Takayasu arteritis were threatened by severe involvement of several vascular segments and had disabling toxic effects from previous treatments. We hypothesized that these patients might benefit from the novel immunosuppressant agent mycophenolate mofetil. Mycophenolate mofetil inhibits the enzyme inosine monophosphate dehydrogenase (a crucial step in the synthesis of guanine nucleotides) and interferes with DNA synthesis. Because lymphocytes depend primarily on de novo purine synthesis while neutrophils use salvage pathways, mycophenolate mofetil specifically inhibits T- and B-lymphocyte proliferation (10).

Mycophenolate mofetil has been used most often in transplant recipients. As several large clinical trials have documented, mycophenolate mofetil is associated with a 60% to 70% greater reduction in the frequency of acute transplant rejection compared with conventional therapies (11, 12). In addition, mycophenolate mofetil shows promise in preventing chronic transplant rejection, which is the major limiting factor for long-term graft survival. In experimental models in rats and primates, mycophenolate mofetil prevents arterial smooth muscle-cell proliferation and proliferative arteriopathy, two mecha-

nisms involved in the chronic transplant rejection process (13, 14). In addition to its use in transplant medicine, mycophenolate mofetil has been used as an immunosuppressive agent in treatment of various diseases, including arthritis and psoriasis. Anecdotal published reports have described the efficacy of mycophenolate mofetil in various immune-mediated diseases, such as systemic lupus erythematosus and the nephrotic syndrome (15).

The rationale for using mycophenolate mofetil in patients with Takayasu arteritis is supported by the drug's immunosuppressive properties and its unique action in preventing lymphocyte-mediated vascular damage. Moreover, mycophenolate mofetil may prove valuable because of its potential for steroid-sparing effects and because it allows patients to avoid the risk for the short- and long-term toxicity associated with cyclophosphamide.

We based our definition of disease activity on clinical and ultrasonographic evaluation. However, the evaluation of the clinical response in Takayasu arteritis is difficult to assess because no accurate definition of disease activity and remission is available; although subjective symptoms, laboratory data, and angiographic changes have been proposed to evaluate disease status, none of them are specific. Therefore, our study is a preliminary report of three patients whom we believed were in danger because of potentially life-threatening complications, such as cerebral ischemia or unbearable side effects of glucocorticoids. A more stringent definition of selection criteria and outcome assessment would be needed in a controlled trial of mycophenolate mofetil in patients with Takayasu arteritis.

All three patients reported a subjective benefit. During the observation period, none experienced new-onset pain in large vessels; clinical examination showed no evidence of new bruits. None of them had fever, and all systemic symptoms resolved. In all patients, tapering or suspension of steroid therapy was achieved. Two patients partially or completely resumed lifestyles they had long abandoned because of their illness. Takayasu arteritis is a remitting and relapsing disease; therefore, we cannot exclude the possibility that our patients' positive response may be due to spontaneous remission rather than the effect of the drug. However, the long history of steroid dependence suggests that the clinical improvement was due to mycophenolate mofetil. A longer follow-up period is needed to assess duration of remission.

We did not perform serial angiographic studies to document disease progression. Instead, we used Doppler ultrasonography evaluation. This is a simple and noninvasive method for monitoring vascular changes, but it has not yet been formally compared with angiography, which remains the gold standard.

In our study, mycophenolate mofetil proved to be safe and well tolerated. None of the patients had leukopenia, thrombocytopenia, or elevated liver enzyme levels; therefore, the dosage of 2 g/d could be maintained throughout the study period. None of the patients reported gastrointestinal discomfort or other clinically significant side effects that could be attributed to mycophenolate mofetil. However, the follow-up may have been too short for more serious adverse effects to have developed.

In conclusion, although the present report is limited by the absence of evidence of angiographic stabilization or regression, the results suggests that mycophenolate mofetil could represent a valid alternative to conventional therapy in patients with Takayasu arteritis. Although the rareness of the disease is an obstacle to designing prospective, controlled clinical trials, this first description of mycophenolate mofetil therapy in patients with Takayasu arteritis is encouraging.

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