Limited Utility of Rapamycin in Severe, Refractory Wegener's Granulomatosis

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ABSTRACT. ***Objective.*** We report our experience using rapamycin in patients with Wegener's granulomatosis (WG) who failed to achieve remission with conventional treatment.

Methods. Eight patients received rapamycin for severe, refractory WG. Clinical outcomes were reviewed retrospectively.

Results. Four patients treated with rapamycin sustained remissions of at least 6 months' duration while receiving prednisone ≤ 10 mg/day; 2 relapsed during followup. Five patients discontinued rapamycin due to continued disease activity, cancer, or adverse events.

Conclusion. Toxicities due to rapamycin were numerous; consistent proof of efficacy in this pilot experience with WG was not seen. (First Release Nov 15 2008; J Rheumatol 2009;36:116–9; doi:10.3899/jrheum.080664)

Key Indexing Terms:
WEGENER'S GRANULOMATOSIS SIROLIMUS

Wegener's granulomatosis (WG) is a systemic inflammatory disease that is histologically characterized by granuloma formation, tissue necrosis, and vasculitis of small- and medium-size blood vessels[1]. WG can affect any organ but has a particular predilection for the upper and lower respiratory tract and kidneys. When untreated, the mean survival time is 5 months[2]. Although cyclophosphamide (CYC) is almost always effective when used in conjunction with corticosteroids (CS), CYC toxicity has encouraged change in this classical approach to treating WG. Current strategies seek to limit CYC exposure or avoid its use altogether. Typical treatment regimens for severe presentations of WG employ a combination of oral, daily CYC and CS for 3–6 months with taper of CS, assuming improvement, after 1 month and continuing over 6 months to the smallest dose needed to maintain remission. After remission is achieved, patients are switched to less toxic maintenance medications such as methotrexate or azathioprine[3,4]. In patients with less severe disease, methotrexate in combination with prednisone may be used to induce remission[5]. However, one-quarter of patients will not achieve a sustained remission of at least 6 months' duration, and at least half will experience irreversible toxicity related to treatment[6,7]. Alternative therapeutics that can induce and maintain remission with less toxicity are needed.

Rapamycin (sirolimus), a macrocyclic lactone, inhibits T and B cell proliferation and activation by arresting lymphocytes in the G1 phase of the cell cycle, and inhibits the translation of mRNA needed for cell growth and proliferation. Rapamycin affects lymphocyte proliferation by inhibiting the function of the mammalian target of rapamycin (mTOR), a regulator of cell proliferation and growth[8], and inhibits the proliferation and differentiation of interleukin 2 (IL-2)-stimulated T lymphocytes[9]. Rapamycin has enhanced organ transplant survival[10-12]. WG is a disease in which enhanced T and B cell activation contributes to pathogenesis[13,14]. The mechanism of action of rapamycin led us to use this agent in patients with WG who had failed to achieve remission or who developed treatment-limiting toxicities from conventional therapies.

MATERIALS AND METHODS

A retrospective chart review was conducted on 8 patients who fulfilled the 1990 American College of Rheumatology criteria for WG[15] and received oral rapamycin between February 1, 2004, and April 1, 2007. To have received rapamycin, patients had to have developed toxicities precluding the use of conventional therapeutics or to have failed to achieve remission

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after receiving a cytotoxic agent plus prednisone that could not be tapered to less than 10 mg/day. A meaningful remission as defined in our previous studies and for purposes of this analysis consisted of the absence of signs or symptoms of active disease, while tapering and maintaining prednisone doses at less than 10 mg/day over a consecutive 6-month period[7].

RESULTS

Eight patients were treated with oral rapamycin with maximum doses of 2–4 mg/day. The median time from disease onset to the start of rapamycin was 6.5 years (range 1–14 yrs). Patients had previously received a median of 4.5 (range 3–8) different immunosuppressive agents in addition to CS prior to the initiation of rapamycin. Features of disease activity that led to the use of rapamycin were multiorgan disease that included lung nodules, chronic unremitting rhinitis, sinusitis or otitis media in the absence of infection, orbital pseudotumor, arthritis, neuropathy, and persistent lacrimal duct inflammation (Table 1). The median Birmingham Vasculitis Activity Score for WG (BVAS/WG) and prednisone dose prior to the start of rapamycin were 3 (range 0–6) and 25 mg/day (range 5–60), respectively. Seven of 8 patients had clinical improvement and were able to taper their prednisone. After 6 months of rapamycin therapy the median BVAS/WG score and daily prednisone dose for all 8 patients were zero (range 0–7) and 11.25 mg/day (range 7.5–35), respectively. No patient was able to discontinue prednisone without disease recrudescence. Four of the 7 patients who had clinical improvement achieved sustained remission, defined as a BVAS/WG score of 0 while taking prednisone doses $\leq$ 10 mg/day for $\geq$ 6 months. Two of the 4 patients who had a sustained remission later relapsed, and one patient stopped rapamycin because of a newly recognized myxofibrosarcoma. The fourth patient continued in sustained remission throughout the period of followup, 30 months. Of the 3 patients who improved but could not achieve a sustained remission $\geq$ 6 months, 2 obtained remission (BVAS/WG = 0) but could not taper their prednisone below 10 mg/day without relapse. The third patient had improvement in BVAS/WG score but could not achieve a complete remission.

Three of 8 patients continued to take rapamycin at the time of chart review; 1 continued in a sustained, prolonged remission. Another relapsed (new lung nodule, sinusitis, and

Table 1. Patient characteristics.

Case	Age, Sex	Prior Therapies (maximum dose)	Failed Therapy at Start of Rapamycin	Past Organ Involvement	Sites of WG Involvement at Time Rapamycin Was Started
1	50 F	Pred (60 mg/day), Solu (1000 mg/day × 3 days), MTX (30 mg/wk), AZA (150 mg/day), CYC (125 mg/day), CYA (200 mg/day, Tac (6 mg/day), Etan (100 mg/wk), Inflix (700 mg/mo), RIT (375 mg/m^2 × 4)	Inflix, CYC, Pred	Sinus, nose, joints, ear, subglottic, lung, lacrimal duct, orbit	Orbit–pseudotumor, lacrimal duct, sinus, joints
2	45 M	Pred (80 mg/day), Solu (1000 mg/day × 3 days), MTX (25 mg/wk), Ada (40 mg/2 wk), AZA (150 mg/day), MMF (2000 mg/day), CYC (150 mg/day)	MTX, Pred	Sinus, nose, joints, skin, eye, neuropathy, ear, oral mucosa, lung	Joints, nose, lung–nodules
3	35 M	Pred (200 mg/day), CYC (150 mg/day), MTX (25 mg/wk), AZA (150 mg/day), RIT (375 mg/m^2 × 4)	RIT	Lung, ear, joints, sinus, nose, kidney eye	Lung–nodules, nose
4	59 F	Pred (60 mg/day), CYC (150 mg/day), MTX (15 mg/wk), AZA (150 mg/day)	AZA, Pred	Lung, joints, sinus, nose, ear, peripheral nerve–neuropathy	Lung–nodules, joints, peripheral nerve–neuropathy
5	62 F	Pred (60 mg/day), MTX (10 mg/wk), AZA (150 mg/day), CYC (200 mg/day), Etan (50 mg/wk), Tac (8 mg/day), Inflix (700 mg/6 wks)	AZA, Pred, Inflix	Ear, sinus, lacrimal duct, eye, lung optic nerve, joints, peripheral nerve–neuropathy	Lacrimal duct, nose, joints, sinus
6	23 F	Pred (40 mg/day), MTX (15 mg/wk), CYC (150 mg/day), AZA (150 mg/day), IVIG (2 g/kg × 2), MMF (2000 mg/day), RIT (375 mg/m^2 × 4), Solu (500 mg/day × 3 days)	Pred, RIT	Kidney, lungs, peripheral nerve–neuropathy, subglottic, sinus, nose, ear, lacrimal duct, gingiva, joints	Nose, sinus, peripheral nerve–neuropathy, joints
7	28 F	Pred (80 mg/day), CYC (100 mg/day), MTX (25 mg/wk), Etan (50 mg/wk), Tac (2 mg/day), AZA (150 mg/day), Solu (1 g/day × 3 day), RIT (375 mg/m^2 × 4)	Pred	Nose, sinus, ear, parotid, arthritis, orbit–pseudotumor, cranial nerve VI, pituitary, lacrimal duct	Orbit–pseudotumor, sinus, ear
8	57 F	CYC (100 mg/day), AZA (100 mg/day), MMF (1000 mg/day), RIT (375 mg/m^2 × 4)	CYC	Skin, joints, breast, kidney, ear, lacrimal duct, sinus, nose, lung–nodule, eye	Lung–nodule

Wk: week, Pred: prednisone, CYC: cyclophosphamide, MTX: methotrexate, AZA: azathioprine, RIT: rituximab, MMF: mycophenolate mofetil, Solu: Solumedrol, Tac: tacrolimus, Etan: etanercept, Inflix: infliximab, CYA: cyclosporine, Ada: adalimumab, IVIG: intravenous immunoglobulin.

arthralgias) after 45 weeks of disease stability. The patient was treated with increased doses of rapamycin and prednisone and improved only temporarily. The third patient had a stable but persistent lung nodule with no other feature of active disease.

For 5 of 8 patients in whom rapamycin was discontinued, 2 patients stopped the drug due to continued disease activity (Table 2). One of the 2 developed new and enlarging cavitating lung nodules and subsequently developed invasive pulmonary aspergillosis. The other had progressive orbital WG. Two patients stopped rapamycin after developing cancer (1 myxofibrosarcoma, 1 cutaneous melanoma). A fifth patient developed pseudomonas pneumonia while receiving rapamycin therapy. Of the 3 patients who had a relapse while receiving rapamycin, each required an additional agent or change in their immunosuppression therapy to achieve remission. Other adverse events attributed to rapamycin that improved with dose reduction included elevated serum transaminase levels (1 patient), oral ulcers (1 patient), and leukopenia (1 patient).

DISCUSSION

The known effects of rapamycin on suppression of both B and T lymphocyte activation made it a theoretically promising agent for WG. Seven of 8 patients with steroid dependency and disease features known to be difficult to control with established therapies initially improved with rapamycin. However, longterm followup was remarkable for disease relapse and numerous adverse events. Chronic CS therapy and longterm treatment with other immunosuppressive agents may have contributed to the high number of adverse events seen in this pilot study.

Limitations to our study include its small sample size and inclusion of patients with disease features that were difficult to control such as orbital pseudotumor and chronic sinusitis.

Whether patients with less severe disease would benefit from rapamycin is not known. While the initial positive response observed in most patients in our cohort might encourage study of rapamycin in less severe or difficult to control cases, the adverse events observed in our cohort advise caution and restraint.

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Table 2. Outcomes related to WG and treatment.

Case	Duration of Rapamycin Treatment (wks)	BVAS/WG Before Start of Rapamycin	Prednisone Dose (mg/day) Before Start of Rapamycin	BVAS/WG 6 mo After Start of Rapamycin	Prednisone Dose (mg/day) 6 mo After Start of Rapamycin	Continued Treatment at Time of Review	Reason for Discontinuing Rapamycin	Adverse Events	Longest Time (wks) in Remission While Receiving Rapamycin
1	153	3	45	2	35	No	Relapse (orbital pseudotumor)	—	65
2	29	3	20	0	17.5	Yes	—	Transient increase in serum transaminase levels	2
3	81	3	5	0	7.5	No	Relapse (lung nodules)	Oral scores, aspergillosis	25
4	35	5	20	1	12.5	No	Shoulder myxofibrosarcoma	—	0
5	123	2	35	0	10	Yes	—	Leukopenia	96
6	35	6	30	7	20	No	Pseudomonas pneumonia	Pseudomonas pneumonia	0
7	33	0	10	0	10	No	Melanoma	—	33
8	46	1	60	0	10	Yes	—	—	14

BVAS/WG: Birmingham Vasculitis Activity Score for WG.

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