

Treatment of Refractory Chronic Urticaria With Sirolimus

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF CASES

CASE 1

A 52-year-old woman with prediabetes reported 5 years of chronic urticaria (CU) with daily flare-ups that had abruptly worsened 1 month previously, with facial angioedema, purpura, wheals lasting longer than 24 hours, and lower limb arthralgias. H₁ and H₂ antihistamines proved ineffective. She had a positive result on the basophil histamine release test (IBT Laboratories, Lenexa, Kansas). She was thought to have urticarial vasculitis (UV) but declined confirmatory skin biopsy. Numerous alternative therapies were unsuccessful (**Table**). She became dependent on prednisone, 20 to 40 mg daily, to remain functional. She developed frank steroid-induced diabetes mellitus, with significant adipose and fluid weight gain, renal hyperfiltration, and dyslipoproteinemia.

CASE 2

A 56-year-old man with hypertension and hypercholesterolemia had had onset of urticaria 3 years prior to presentation. H₁ and H₂ antihistamines and montelukast sodium reduced CU outbreaks to several days a week, but severe breakthroughs still occurred regularly. Oral corticosteroids yielded partial control. Because there was no clinical evidence of UV, a skin biopsy was not performed. Of alternative agents tried, he showed only initial improvement from the use of mycophenolate mofetil. He declined to increase the dose as planned, even as his CU relapsed after several weeks and again became intractable.

CASE 3

A 43-year-old woman had first developed urticaria and angioedema 1 year previously; it had begun and remitted that autumn. At presentation during that time, lesions had lasted more than 24 hours and had been accompanied by bruising but no systemic symptoms. Combination antihistamines and montelukast demonstrated no efficacy. Skin biopsy confirmed UV, and basophil histamine release was also positive. She initially responded to combination hydroxychloroquine sulfate

and colchicine, but there was suspicion that the remission was spontaneous due to her previous pattern. She remained medication-free until the following autumn, when her UV reappeared. She was restarted on hydroxychloroquine and colchicine but failed to respond or remit spontaneously. Prednisone, up to 40 mg daily, was required to maintain control.

THERAPEUTIC CHALLENGE

Chronic urticaria is defined as at least 6 weeks of daily or nearly daily typical wheals. Urticarial vasculitis exhibits a more severe course. Lesions last more than 24 hours and may be accompanied by purpura, systemic symptoms, and histopathologic evidence of vasculitis. An increasingly recognized clinical problem is refractoriness to standard antihistamine-centered regimens. Current practice in addressing this important subpopulation comprises trials of various alternative therapies, as recently reviewed.^{1,2} However, despite numerous such agents being available, no single therapy is recognized as being highly effective, reliable, safe, convenient, and inexpensive.

Table. Other Alternative Therapies Tried by Patients in This Study^a

Drug	Regimen	Cases in Which Drug Used
Montelukast sodium	10 mg daily	1, 2, 3
Dapsone	100 mg daily	1, 2, 3 ^b
Hydroxychloroquine sulfate	200 mg twice daily	1, 2, 3
Colchicine	0.6 mg twice daily	1, 2, 3
Olsalazine sodium	500 mg twice daily	1, 2
Mycophenolate mofetil	250 mg twice daily for about 1 wk, then titrating up to 500 mg twice daily	1, 2, 3 ^c
Celecoxib	100 mg twice daily	3
Etanercept	25 mg subcutaneously twice weekly	3

^a All trials lasted 4 weeks, unless otherwise specified.

^b Patient 1 discontinued dapsone therapy after several days owing to drug rash.

^c Patient 2 declined to increase dosage until second trial period after finishing sirolimus.

SOLUTION

Oral medications used to prevent organ allograft rejection have been used successfully in the setting of refractory CU.¹ Cyclosporine has been best studied,³⁻⁵ but reports have also suggested that tacrolimus⁶ and mycophenolate mofetil⁷ were promising. Sirolimus is used as an alternative to or alongside calcineurin inhibitors in a variety of applications, including transplantation and cutaneous disorders.⁸ Based on parallels in the immunologic properties and applications of these agents and differences in adverse effects, sirolimus was offered to these 3 patients as an alternative to calcineurin inhibitors.

In case 1, the patient, after a 6 mg loading dose, was started on 1 mg daily, which allowed rapid reduction of prednisone below 10 mg daily over the following month. Sirolimus was then increased to 1 mg twice daily; during the following month, she stopped prednisone completely. Sirolimus was continued another month at this dose and then tapered off over an additional month without recurrence of urticaria. Leg edema improved when sirolimus was stopped. She has had drug-free remission for 1 year now.

In case 2, the patient had mild, self-limited alimentary symptoms after the 6 mg loading dose of sirolimus. Within the first week at 1 mg twice daily he noted distinct resolution of urticaria, which had, up to that point, broken through prednisone. Despite stopping prednisone, total clearance of urticaria persisted. Sirolimus was then stopped after 2 months of therapy at 1 mg twice daily due to bothersome leg swelling. He remained symptom free for 2 months but then experienced gradual recurrence. However, he declined to restart sirolimus due to fear of leg swelling and elected to be maintained on partial control with a higher dose of mycophenolate mofetil.

In case 3, the patient was started on sirolimus, as previously described. After 2 months she showed no significant steroid-sparing effect, which we considered a clinical failure. She declined to try advancing the dose beyond 3 mg daily. She was then started on etanercept, which abolished severe exacerbations but did not completely relieve daily symptoms.

COMMENT

In the 3 cases presented, sirolimus shows promise as a new option in managing severe CU and UV that have proven refractory to first-line and other agents. Adjunctive treatments were reasonably standardized prior to starting sirolimus, namely, failure of combination antihistamines and numerous less expensive or less toxic alternative agents. Examples of drug-free remission, clinical benefit but intolerance of side effects, and lack of significant response are represented in this series of all patients with CU or UV I have thus treated to date. Similar to calcineurin inhibitors, reliability in producing clinical benefit will not be 100%: some failure rate should be expected.

Both responders exhibited a clear steroid-sparing effect, rendered more remarkable by incomplete response at baseline to moderate-dose prednisone that evolved into com-

plete clinical remission soon after starting sirolimus. Drug-free remission, in many ways the holy grail of urticaria management, has been observed in some CU patients taking calcineurin inhibitors.^{4,9} It appears that sirolimus might share this advantage. Variability of disease over time is a problem in the investigation of the efficacy of interventions in CU and UV. However, the abrupt cessation of all symptoms in the expected time frame (ie, response time comparable to cyclosporine¹⁰) and, in one responder, a dose-response effect support some role for sirolimus in achieving remission.

No serious adverse effects were observed with the moderate doses and short durations typical of urticaria applications. Leg swelling was observed in 2 patients and of sufficient severity that one chose to avoid future use despite excellent clinical results. Major adverse effects include headache, alimentary complaints, extremity edema, rash, tremor, arthralgias, fatigue, weight gain, dyslipoproteinaemia (probably to a lesser degree than would be expected with a regimen of cyclosporine), cytopenias, and immune suppression-related neoplasia or infections. Sirolimus is a substrate of cytochrome P450 3A4, which may give rise to important drug interactions. As with other alternative agents,¹¹⁻¹³ urticaria, angioedema, and drug rash have been reported as adverse effects, mainly in renal transplant recipients.¹⁴ Laboratory monitoring included baseline blood counts, renal function, and hepatic enzymes and interval blood counts. Weight, fluid status, and evidence of infectious complications were also assessed.

The ultimate role of sirolimus in the management of refractory CU and UV remains to be determined. Assuming that sirolimus shares comparable efficacy with calcineurin inhibitors, to have this additional option to offer frustrated patients and clinicians would be a welcome prospect. Compared with the calcineurin inhibitors, different intracellular binding targets are responsible for the distinct mechanism of action and side effects of sirolimus, although both have overlapping indications and immunologic properties. Whereas calcineurin inhibitors block production of interleukin-2, sirolimus inhibits the response to interleukin-2, thus inhibiting activation of B- and T-lymphocytes. As in other applications, differences in adverse effects and efficacy may thus become apparent between sirolimus and parallel medications, which will lead to better design of therapeutic regimens. Future investigation of sirolimus should be considered for CU and UV patients, especially randomized controlled trials and even comparative studies with calcineurin inhibitors.

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Submissions

Clinicians, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Manuscripts should be prepared double-spaced with right margins nonjustified. Pages should be numbered consecutively with the title page separated from the text (see Instructions for Authors [<http://archderm.ama-assn.org/misc/ifora.dtl>] for information about preparation of the title page). Clinical photographs, photomicrographs, and illustrations must be sharply focused and submitted as separate JPG files with each file numbered with the figure number. Material must be accompanied by the required copyright transfer statement (see authorship form [http://archderm.ama-assn.org/misc/auinst_crit.pdf]). Preliminary inquiries regarding submissions for this feature may be submitted to George J. Hruza, MD (ghruza@aol.com). Manuscripts should be submitted via our online manuscript submission and review system (<http://manuscripts.archdermatol.com>).