



Letter

Clinical and biological response to rituximab treatment in 3 patients with acquired C1-inhibitor deficiency

Acquired C1 inhibitor (C1-INH) deficiency (ACID) is a rare cause of recurrent subcutaneous and submucosal edema without urticaria. The mechanisms of ACID include excessive C1-INH consumption because of an underlying lymphoid malignant tumors (often undiagnosed) or the presence of anti-C1-INH autoantibodies, often with an isolated monoclonal gammopathy or a lymphoproliferative disorder.^{1–3} The primary therapy for ACID is treatment of the underlying condition; however, management is complex, and all patients must have a medication for acute angioedema. Options for acute attacks include replacement C1-INH or bradykinin inhibitors (eg, icatibant or ecallantide). Some patients may also benefit from prophylactic therapy, including replacement C1-INH, attenuated androgens, or antifibrinolytics. Although antifibrinolytics decrease angioedema attacks in ACID,^{1–3} they may increase the risk of a thromboembolic event. Several case studies and retrospective data on ACID cohorts have found that rituximab is an effective treatment in some but not all patients.^{1–9} Predicting who will respond is difficult and may depend on the presence of anti-C1-INH antibodies or an underlying malignant tumor. In addition, whether the clinical response to rituximab matches the biologic response (ie, normalization of C4, C1-INH antibodies, C1-INH function and/or protein) has been reported in some of these studies but with varied findings.^{4–9} In this report, we describe 3 patients who received courses of rituximab (defined as cycles of 4-weekly infusions, 375 mg/m²) with the goal to determine whether the clinical response matches the biologic response.

Patient 1 is a 60-year-old woman who presented with 1½ years of nearly monthly severe lower quadrant abdominal pain and an unexplained 25-lb weight loss. Her evaluation revealed normal colonoscopic findings; abdominal computed tomography during an attack revealed mesenteric swelling. A follow-up bone marrow biopsy identified a low-grade B-cell lymphoma, and observational therapy was recommended. Serum test results were consistent with ACID (Table 1). She was prescribed icatibant for attacks and aminocaproic acid for prophylaxis, which reduced her attack frequency (approximately 50%) and severity. She subsequently developed thrombocytopenia, secondary to spleen enlargement from her B-cell lymphoma, and received a course of rituximab. A subsequent bone marrow biopsy revealed mild residual B-cell lymphoma, for which she received a second rituximab course. Twelve months later, she has only experienced one episode of abdominal angioedema, her C1-INH function normalized, her C1-INH antigen has approached normal, and her C4 remained unchanged.

Patient 2 is a 64-year-old woman who developed lip swelling 12 hours after shellfish ingestion (previously tolerated), with minimal improvement from antihistamine treatment. She also had intermittent abdominal pain (approximately every 3–4 months) that lasted 2 to 4 days for the past 1½ years. Her evaluation included normal endoscopy results, undetectable shellfish IgE, and serum test results that confirmed ACID (Table 1). She was prescribed icatibant for acute angioedema. Further evaluation for an underlying malignant tumor included abdominal computed tomography, which revealed splenomegaly, and a bone marrow biopsy consistent with marginal zone lymphoma. She received one rituximab course; after more than 12 months, she has not experienced angioedema or abdominal pain, despite a persistently low C4 level and C1-INH protein and function.

Patient 3 is a 82-year-old man who was referred for recurrent angioedema without urticaria. His initial episodes were mild extremity swelling, which resolved without treatment. He then experienced an episode of airway swelling for which he was administered epinephrine, corticosteroids, and antihistamines without improvement. He refused intubation, and his symptoms resolved in 24 hours. His laboratory work was consistent with ACID (Table 1) and monoclonal gammopathy. Results of a bone marrow biopsy were unremarkable. He was prescribed danazol for prophylaxis and plasma-derived C1-INH for rescue. He initially did well but began to experience severe weekly breakthrough facial and tongue attacks. Neither increasing the danazol dosing nor changing to aminocaproic acid improved his symptoms. He received a course of rituximab, decreasing his attack severity and frequency (4 attacks) in the next 12-months, at which time his facial attacks returned. He received a second rituximab course, again decreasing his attack severity and frequency and normalizing his C1-INH protein level. Eighteen months later, despite prophylactic treatment with plasma-derived C1-INH, his symptoms returned with nearly weekly attacks, which responded to both icatibant and plasma-derived C1-INH. He will undergo a third rituximab course. Rituximab treatment did not alter his C1-INH antibody or C4 levels.

Our 3 patients reaffirm the variability and difficulty in predicting outcomes of rituximab treatment for ACID as reported by others. Previous work has not found consistent clinical or biological factors to *predict* the response to rituximab, which is critical because it is an immunosuppressant. We evaluated whether the clinical and biologic responses to rituximab correlate with each other and found inconsistencies in these responses. Patient 1 had a clinical and biologic response, patient 2 had a clinical but not a biologic response, and patient 3 had a relapsing clinical response, without a biological response. Like other reports, some patients may require an additional cycle of rituximab to achieve

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Table 1
Clinical and Biologic Response to Rituximab

Characteristic	Patient 1	Patient 2	Patient 3
Rituximab cycle number ^a	2	1	2
Underlying cause	B-cell lymphoma	Marginal zone lymphoma;	Monoclonal gammopathy
Treatment before rituximab			
Prophylaxis	Aminocaproic acid	None	Danazol, aminocaproic acid
On demand	Icatibant	Icatibant	pdC1-INH
C1-INH antigen, mg/dL (reference range, 21–39 mg/dL)			
Initial	3	5	15
After first cycle	5	6	ND
After second cycle	18	NA	25
C1-INH function, % (reference range, ≥60%)			
Initial	17	<40	13
After first cycle	18	18	ND
After second cycle	90	NA	4
C4, mg/dL (reference range, 10–40 mg/dL)			
Initial	1	4	5
After first cycle	<5	<5	ND
After second cycle	1	NA	<3
C1q, μg/mL (reference range, 109–242 μg/mL)			
Initial	<3.6	3.6	7.7
After first cycle	9.6	<50	ND
After second cycle	<50	NA	146
Anti–C1-INH autoantibody			
Initial	ND	ND	Positive
After first cycle	ND	ND	Positive
After second cycle	ND	ND	Positive
Clinical outcome (follow-up time)	1 attack (>12 mo)	No attacks (>12 mo)	Weekly attacks
Continued treatment			
Prophylaxis	Amicar	None	Danazol, amicar, pdC1-INH
On demand	Beriner, icatibant	Icatibant	beriner, icatibant
			None

Abbreviations: C1-INH, C1 inhibitor; NA, not applicable; ND, not determined; pdC1-INH, plasma-derived C1 inhibitor.

^aAll cycles were weekly infusions of 375/mm³ for 4 weeks.

clinical improvement. Our third patient may benefit from maintenance rituximab therapy but not without the potential for adverse outcomes associated with sustained B-cell suppression. Our findings are similar to previous single patient cases reports, with some reporting clinical and biological improvements^{4,5} or a clinical but not biologic change^{6,7} after rituximab therapy. In larger reports, Levi et al⁹ described 3 patients, all of whom developed clinical improvement (2 with normalization of C1-INH function and C4 level). Branellec et al⁸ described 7 patients, 3 with full clinical response (2 with normalization of C1-INH antigen but not function), 2 with partial clinical response (without biologic response), and 2 without clinical or biologic response.

Although some patients with ACID benefit from rituximab to achieve suppression of angioedema, and it is an option for those refractory to C1-INH replacement, antifibrinolytics, or anti-bradykinin therapies, our 3 patients illustrate the difficulties in determining its clinical response based on follow-up biological markers after therapy. Our case report, like others, also shows that some patients may require more than 1 treatment cycle. In those patients, the potential adverse effects of rituximab (ie, B-cell depletion, potential for hepatitis B reactivation in those positive for hepatitis B surface antigen or hepatitis B core antibody, prolonged hypogammaglobulinemia) should be monitored, similar to patients receiving rituximab for other disorders.¹⁰ The long-term follow-up of patients with ACID receiving rituximab who have clinically responded to it requires further study to determine whether the clinical response persists. Nevertheless, these patients should retain access to rescue medications for angioedema. In summary, our report adds to the literature data on the treatment outcomes of a rare disorder, ACID, and the complexities involved in predicting its treatment response to rituximab.

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