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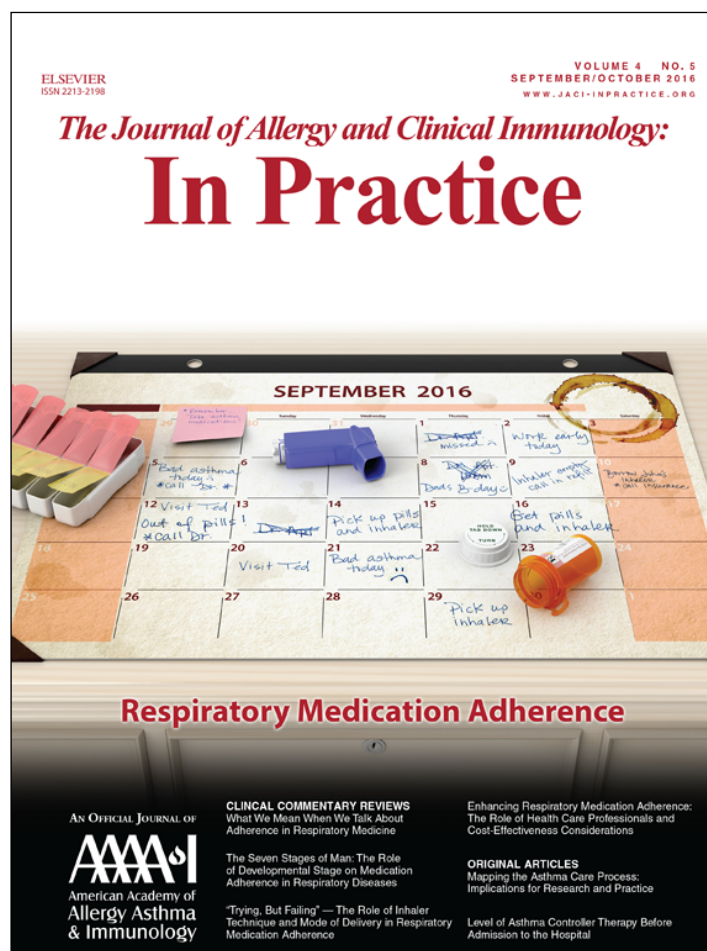


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Clinical Communications

Skin testing, graded challenge, and desensitization to von Willebrand factor (VWF) products in type III von Willebrand disease (VWD)



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Clinical Implications

- This is the first report of skin testing, graded challenge, and desensitization for von Willebrand factor (VWF) replacement products in patients with VWF deficiency. Patients who have experienced reactions to VWF products may benefit from these protocols.

TO THE EDITOR:

Von Willebrand disease (VWD) is the most common inherited disorder of hemostasis, which affects approximately 1 in 1000 individuals in the population. VWD is caused by defects in the quantity or quality of von Willebrand factor (VWF), a multimeric glycoprotein that binds to collagen and platelets on activation, which leads to hemostasis. Clinical manifestations vary greatly between patients, and can range from mild mucocutaneous bleeding to musculoskeletal bleeding and stroke.^{1,2}

Type III VWD is the most severe form of the disorder and can be fatal. It affects approximately 1 in 1 million live births.¹ For these severe cases of VWD, there are a variety of VWF replacement products. Unfortunately, a small number of patients, generally those with severe deleterious mutations, develop alloantibodies (most commonly polyclonal IgG) to such products, with estimates ranging from 5.8% to 9.5%.^{3,4} Such antibodies, called inhibitors, reduce or eliminate the hemostatic response that typically accompanies infusion. Immune tolerance induction was reported to successfully eradicate inhibitors in a case report from 2012.⁵ There have also been reports of patients experiencing symptoms consistent with anaphylaxis when exposed to VWF or factor VIII replacement products (some of which contain VWF).³⁻⁶ Prior studies have identified immune complex formation and complement activation as mediators of these reactions, rather than IgE.³ Here, we describe 2 patients with VWD with inhibitory alloantibodies to VWF who developed VWF infusion reactions, some of which were clinically consistent with anaphylaxis given documentation of urticaria, respiratory distress, and hypotension. Evaluation and treatment was ultimately made possible through skin prick and intradermal testing, graded challenge, and/or desensitization.

Patient 1 is a 2-year-old boy from the United Arab Emirates who is one of several affected siblings with type III VWD from a consanguineous marriage. Genetic analysis revealed a large deletion in the *VWF* gene (c.658_7887del: p.G220_L2629del). He required frequent VWF replacement infusions for recurrent bleeding episodes. Given the high frequency of these bleeding episodes and a family history that included the death of an older

brother from a brain hemorrhage at 7 months of life, prophylactic VWF infusions were ultimately recommended.

Unfortunately, the patient began experiencing worsening hypersensitivity reactions once prophylactic Wilate (a plasma-derived VWF replacement product) treatments were initiated at 20 months of age. Before coming to our center for treatment, the patient had received approximately 15 infusions. The family reported allergic reactions to the most recent infusions but could not fully characterize the details of these reactions. Three separate reactions to Humate-P (another plasma-derived VWF replacement product) were subsequently documented in our infusion center. These reactions were characterized by shortness of breath, urticaria, tachycardia, and mild hypotension that occurred within 5 minutes of starting an infusion (infusions were scheduled to run over 10 minutes). Infusions were stopped before completion in 2 of the 3 cases. Each reaction was treated with IV diphenhydramine with good effect and symptoms lasted for no longer than 90 minutes after this treatment. In addition to these reactions, reduced efficacy of VWF replacement therapy was observed because of the development of VWF inhibitory alloantibodies. The presence of such inhibitors was subsequently confirmed via ELISA, which documented anti-VWF antibodies at 142.3 standard deviations above mean levels in healthy controls.

An evaluation and treatment plan was therefore devised to address the patient's hypersensitivity reactions so that an induction of tolerance protocol could be implemented to potentially reduce the inhibitors. First, skin prick and intradermal testing (Table I) was performed to evaluate for IgE-mediated allergy, and if so, whether the reactions were specific to VWF versus another component in the VWF replacement preparation. In addition to the VWF replacement products (Humate-P and Wilate), polysorbate 80 and multiple factor VIII products were tested. (Polysorbate 80 is an emulsifier used in the Wilate preparation, which has also been reported to lead to hypersensitivity reactions.⁷ Factor VIII is present in all VWF preparations.) Skin testing was negative to both VWF products, factor VIII, and polysorbate 80 at the highest concentrations tested. Two healthy volunteers who were not previously exposed to these medications were also tested and did not have reactions to any of the medications at these highest concentrations on both prick and intradermal testing.

Despite the fact that no IgE-mediated mechanism could be confirmed, given the severity of his reactions and the requirement for treatment, desensitization to Wilate was performed after premedication with diphenhydramine (Table II). The patient tolerated the procedure without incident. He was initially put on a regimen of daily Wilate infusions to maintain the desensitized state, and to complete an induction of tolerance protocol. He did well on this regimen and transitioned to receiving Wilate infusions every other day at age 4. The patient has not had hypersensitivity reactions after desensitization.

The patient's older brother, patient 2, presented to us at 8 years of age. He also had type III VWD and required frequent infusions with VWF replacement products. Like his younger brother, prophylactic VWF infusions were recommended. Unfortunately, the patient began experiencing shortness of breath

TABLE I. Skin prick and intradermal testing concentrations

Product	Skin prick test	Intradermal 1	Intradermal 2
Wilate	VWF 100 IU/mL, FVIII 100 IU/mL	VWF 10 IU/mL, FVIII 10 IU/mL	VWF 100 IU/mL, FVIII 100 IU/mL
Humate-P	VWF 120 IU/mL, FVIII 50 IU/mL	VWF 12 IU/mL, FVIII 5 IU/mL	VWF 120 IU/mL, FVIII 50 IU/mL
Helixate	300 IU/mL	30 IU/mL	300 IU/mL
Advate	300 IU/mL	30 IU/mL	300 IU/mL
Xyntha	300 IU/mL	30 IU/mL	300 IU/mL
Monoclate	300 IU/mL	30 IU/mL	300 IU/mL
Polysorbate 80	100 mg/mL	0.1 mg/mL	1 mg/mL

FVIII, Factor VIII; VWF, von Willebrand factor.

Both patients and controls had negative reactions to all concentrations used for skin prick and intradermal testing. All products were reconstituted in the diluent supplied by the manufacturer, but subsequently further diluted for skin testing reagents using saline.

TABLE II. Twelve-step desensitization protocol to Wilate

Full therapeutic dose:	435 IU daily
Premedication:	Diphenhydramine: 1 mg/kg mg PO, 1 h before start of desensitization and 1 h before each subsequent dose

A. Prepared solutions

Solution	cc/bag	IU/bag*	IU/mL
1	250	4.35	0.017
2	250	43.5	0.174
3	250	431.6	1.726

B. Desensitization

Step	Solution	Rate (cc/h)	Time (min)	Dose (IU)	Cumulative dose (IU)
1	1	2	15	0.009	0.009
2	1	5	15	0.022	0.031
3	1	10	15	0.044	0.074
4	1	20	15	0.087	0.161
5	2	5	15	0.218	0.379
6	2	10	15	0.435	0.814
7	2	20	15	0.870	1.684
8	2	40	15	1.740	3.424
9	3	10	15	4.316	7.739
10	3	20	15	8.632	16.371
11	3	40	15	17.263	33.634
12	3	75	186	401.37	435.000
Total time		351 min			

*The total IU used for preparation is more than the final dose because solutions 1 and 2 are not completely infused.

associated with infusions of both Wilate and Humate-P at 7 years of age. Unlike his brother, who had multiple classic symptoms of a hypersensitivity reaction, this patient's symptoms were limited to reports of difficulty breathing and mild tachypnea with respiratory rates up to 25 breaths per minute. This respiratory distress occurred within minutes of starting the infusions and was often severe enough that the infusions were stopped. Like his brother, the patient also developed VWF inhibitors that reduced the efficacy of VWF replacement. This was confirmed by ELISA, which documented anti-VWF antibodies at levels 89.9 standard deviations above mean levels in healthy controls.

To assess whether symptoms were due to an IgE-mediated mechanism, the patient had skin prick testing to various

components of his VWF replacement therapy (Table I). Skin testing was negative to both VWF products, factor VIII, and polysorbate 80.

As the patient's tachypnea may have been related to anxiety, and also given no other clinical evidence of hypersensitivity reaction and negative skin testing, he underwent graded challenge to Wilate (starting dose 1/100th of the full dose, followed in 30 minutes by 1/10th of the full dose, followed in 30 minutes by 9/10th of the full dose). He tolerated this without any reactions. An induction of tolerance protocol, which consisted of every other day dosing of Wilate, was therefore initiated in an attempt to reduce titers of VWF inhibitors. The patient then began developing significant back pain with these infusions that only partially subsided when the infusions were run at a lower rate. The back pain entirely resolved once infusions were transitioned from every other day to daily. He continued on daily maintenance infusions with VWF until age 10, when he was again transitioned to receiving infusions every other day. He has tolerated this well with no further reactions.

We describe 2 cases of type III VWD where administration of VWF was limited due to infusion reactions. Although the reactions had features of an IgE-mediated mechanism, including shortness of breath, urticaria, tachycardia, and mild hypotension, in both cases skin prick testing was negative, which suggested a non-IgE-mediated mechanism. Unfortunately, tryptase levels, which may have been helpful in better characterizing these reactions, were not drawn during any of these episodes. Overall, our findings are consistent with previous reports describing anaphylaxis to VWF replacement products in patients with inhibitors.³ These reports have suggested that immune complex formation and complement activation mediate life-threatening symptoms rather than IgE, though skin testing was not performed.³ Of note, the patients reported here had hypersensitivity reactions to the plasma-derived VWF replacement products (Wilate and Humate-P). We are not aware of evidence that would suggest that generation of inhibitor antibodies or hypersensitivity reactions would differ depending on whether a patient received plasma-derived preparations or a recombinant VWF product such as Vonvendi, which was not available in the United States at the time these patients were treated.

We report a successful desensitization protocol for VWF replacement that was tolerated without any reactions, though the patient had negative skin testing to this factor. This is consistent with previous reports of utilization of such procedure in some other cases of non-IgE-mediated drug reactions.^{8,9} To our knowledge, this is the first report of skin testing, graded challenge, and

desensitization protocols to VWF products. These procedures and protocols may be of benefit in other patients with reactions to VWF products. Furthermore, this study supports a role for desensitization in non—IgE-mediated reactions to VWF products.

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