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Hypersensitivity reaction to intravenous but not oral tacrolimus

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Overcoming drug hypersensitivity reactions can improve transplant patient care, especially when specific medications are integral to treatment protocols. Our allergy service was consulted on a 40-year-old female hematopoietic stem cell transplantation (HSCT) patient for a hypersensitivity reaction during intravenous (IV) tacrolimus infusion. The patient was recently diagnosed with AML M5a and was status-post induction chemotherapy in her first complete remission. She was admitted for a myeloablative allogeneic HSCT and was under a randomized transplant protocol that included tacrolimus to prevent graft versus host disease (GVHD).

The patient had never received tacrolimus. Within five minutes of her first IV dose, she developed pruritus, nausea, vomiting, and diffuse urticaria. She had no other symptoms. Her pulse increased to 102/min, but her blood pressure and oxygen saturation remained stable. The infusion was stopped within 15 minutes. She had not received any other medications. She was administered 50 mg of IV diphenhydramine with resolution of her symptoms. We were consulted for recommendations regarding future dosing of tacrolimus.

Tacrolimus intravenous infusion contains anhydrous tacrolimus, polyoxyl 60 hydrogenated castor oil (HCO-60), and dehydrated alcohol (Table 1). Polyoxyl 60 hydrogenated castor oil (HCO-60) is a form of polyoxyethylated castor oil solubilizer similar to Cremophor. Cremophor is a nonionic surfactant obtained by polyethoxylation of castor oil expressed from the seed of *R. communis*, and it is used as a solubilizer in several medications (1). It has been associated with hypersensitivity reactions with medications including vitamin K, cyclosporine, paclitaxel, diazepam, propanidid and multivitamin hydrosol (2, 3). Oral tacrolimus does not require a solubilizer and consequently does not contain polyoxyethylated castor oil (Table 1).

Our patient's symptoms were consistent with a hypersensitivity reaction. Our suspicion was that her reaction was to the intravenous carrier polyoxyethylated castor oil and not to tacrolimus itself. Since the oral form of tacrolimus does not contain polyoxyethylated castor oil, we recommended a two step graded challenge with oral tacrolimus. The patient tolerated

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oral tacrolimus without reaction and was maintained on oral tacrolimus without any complications.

The intravenous forms of both tacrolimus and cyclosporine contain polyoxyethylated castor oil (Table 1). Both have oral counterparts that do not. There are case reports describing patients who react to intravenous cyclosporine but tolerate the corn-oil based soft gelatin capsule formulation of cyclosporine (Sandimmune soft gelatin capsule formulation, Novartis)(2, 3). Takamatsu et al(3) describe a patient with T cell lymphoma status post allogeneic HSCT who developed diffuse urticaria and tachycardia within minutes of receiving a first lifetime dose of intravenous cyclosporine. Intravenous tacrolimus was then tried which also resulted in diffuse urticaria. The patient was then started on the oral soft gelatin capsule cyclosporine formulation and had no reaction. Volcheck et al(2) report a patient with AML status post HSCT who developed urticaria, angioedema, vomiting, and throat tightness with his first lifetime dose of intravenous cyclosporine, but who later tolerated the oral soft gelatin capsule formulation of cyclosporine. They also performed a literature search which revealed 22 cases of IV cyclosporine hypersensitivity reaction. Seven of these patients were subsequently given oral formulations of cyclosporine which they tolerated.

The common chemotherapy agent paclitaxel is another example of a drug that contains a carrier that is thought to be responsible for hypersensitivity reactions rather than the drug itself. Consequently, Abraxane (nab-paclitaxel), a Cremophor-free formulation of paclitaxel, has been developed and five patients with hypersensitivity reactions to paclitaxel tolerated Abraxane without incident (4).

Proposed mechanisms underlying hypersensitivity reactions to polyoxyethylated castor oil include IgE-mediated (2), complement activation (5) or direct histamine release (6). IgE mediated reactions typically require prior exposure for sensitization. Though our patient had never received intravenous tacrolimus, polyoxyethylated castor oil is used as a vehicle in several medications and she may have been exposed to the carrier previously. While a method to investigate IgE mediated reaction is to perform a skin test to the suspected allergen, this was not appropriate in our patient's clinical situation, and there is no validated skin test for polyoxyethylated castor oil allergy.

To our knowledge, this is the first report of tolerance to oral tacrolimus following a hypersensitivity reaction to IV tacrolimus. Our experience suggests that polyoxyl 60 hydrogenated castor oil was the culprit agent. Oral tacrolimus formulations should therefore be considered as an alternative in patients who have reacted to IV tacrolimus. This is especially important in the transplant population who require immunosuppression. Of note, Jina Pharmaceuticals manufactures an intravenous tacrolimus formulation (Nanosomal Tacrolimus) that does not contain polyoxyethylated castor oil, but it is not currently available for clinical use(7).

Abbreviations

AML	Acute Myeloid Leukemia
GVHD	Graft versus host disease
HSCT	Hematopoietic stem cell transplantation
HCO-60	Polyoxyl 60 hydrogenated castor oil

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Table 1

Components of tacrolimus and cyclosporine formulations

IV Tacrolimus (Prograf)	Oral Tacrolimus (Prograf)	IV Cyclosporine (Sandimmune)	Oral Cyclosporine (Sandimmune soft gelatin capsule)
<ul style="list-style-type: none"> • Tacrolimus • Polyoxyl 60 hydrogenated castor oil (HCO-60) • Dehydrated alcohol 	<ul style="list-style-type: none"> • Tacrolimus • Lactose monohydrate • Hypromellose • Croscarmellose sodium • Magnesium stearate 	<ul style="list-style-type: none"> • Cyclosporine • Polyoxyl 35 castor oil (Cremophor EL) • Dehydrated alcohol 	<ul style="list-style-type: none"> • Cyclosporine • Corn Oil (Labrafil M 2125 – polyoxyethylated glycolysed glycerides) • Linoleoyl macroglycerides • Gelatin • Iron Oxide Red • Sorbitol • Titanium dioxide