

sometimes GI diseases are not controlled well with IVIG replacement, because these preparations contain IgG which cannot reach the lumen of the intact gut and also contain very little amount of IgA which is a vital component of mucosal defence.^{5,6} Recent experimental evidence suggests that IVIG could exert an effect more than passive substitution of antibodies could do against pathogenic microbes; it rectifies the defective signalling and induces an optimal functioning of cellular compartment, thus re-establishing immune homeostasis.⁷ Theoretically, treatment with oral immunoglobulin has not been successful, because IgG is rapidly destroyed before reaching the small intestine. There is an animal study, which showed an induction of oral tolerance by oral administration of IVIG against anti-phospholipid syndrome in naïve mice.^{5,6,8} The presented case is a unique one, since the patient experienced improvement of chronic diarrhoea following oral administration of IVIG. Our results point to a possible role of oral IVIG in the improvement of chronic diarrhoea in CVID patients, especially in those infested by organisms such as *Giardia*. However, further original multi-centre studies are needed to test the efficacy of oral administration of immunoglobulin in improvement of diarrhoea severity in those with CVID.

Ethical disclosure

Confidentiality of data. The authors declare that no experiments were performed on humans or animals for this investigation.

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of interest

The authors have no conflicts of interest and no funding was received.

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Desensitisation of the youngest patient with Pompe disease in response to alglucosidase alfa

To the Editor,

Biological agents such as cytokines, monoclonal antibodies and enzymes can cause allergic reactions, which may result in a wide range of clinical symptoms, from light pruritus to anaphylactic shock.¹ Hypersensitivity reactions

increase as exposure to biological agents increases.² One biological agent that may cause a hypersensitivity reaction is recombinant human acid α -glucosidase (rhGAA). rhGAA is used to treat Pompe disease (PD),³ which is a rare, progressively debilitating, and often fatal lysosomal storage disorder. Enzyme replacement therapy (ERT) with rhGAA is shown to improve cardiomyopathy, motor skills, and functional independence, and to prolong survival in patients with PD.⁴ Other than rhGAA, there are currently no alternative treatments for PD.⁴ The present paper proposed a new desensitisation protocol that follows general desensitisation

rules. The protocol was applied to the youngest patient with PD who developed anaphylaxis in response to rhGAA.

This seven-month-old female was born after an uneventful pregnancy. Her parents were first-degree cousins. The patient was diagnosed prenatally with PD after the death of her older brother from PD. Postnatal DNA sequence analysis of the GAA gene revealed homozygous c.1195-2A>G mutation which was previously shown to cause severe infantile PD.⁵ The cross-reactive immunological material (CRIM) status of the patient was determined by Western blot analysis and was found positive. The patient's brother was treated as a newborn at another medical centre for poor sucking, hypotonia, and cardiomegaly in 2005. He was diagnosed with PD following laboratory testing, including enzyme measurements and a muscle biopsy. The patient's brother died at eight months of age as a result of cardiopulmonary failure. Moreover, a cousin of the patient's father was also diagnosed with PD and died at four months of age. The patient's relatives were not treated with ERT because it was not available then. The female patient was started on the standard dose of rhGAA at another centre during her first month of life. During this period, the patient was asymptomatic; however, a low α -glucosidase alfa level, high serum creatinine kinase level, and interventricular septal hypertrophy were noted. Anaphylactic shock developed after 15 min in response to the twelfth ERT session. Widespread erythema on the ears, back, and chest were noted, as well as irritability and an intractable cough and stridor. A light erythema and generalised itching had been reported during the previous ERT session. Upon admission to our department, the patient's growth and physical examination were normal. Following echocardiographic examination, hypertrophy in the interventricular septum and mild tricuspid regurgitation was observed. The patient and the family had no history of atopy. Epidermal tests with rhGAA at concentrations of 1:1000 and 1:100 were negative five weeks after the anaphylaxis. Intradermal test with rhGAA at a concentration of 1:1000 was applied and was positive, with 6-mm $\times$ 6-mm induration and surrounding hyperaemia. Therefore, we decided to treat the patient with desensitisation to rhGAA. We started the desensitisation protocol with half of the standard dose (i.e., 10 mg/kg) as previously reported^{6,7} and gave this dose once a week instead of the standard recommended dose every two weeks (Table 1). Six different concentrations of rhGAA solution were prepared ranging from the stock solution of 5 mg/ml to a saline-diluted concentration of 0.05 μ g/ml. A seventh concentration of 1 mg/ml was also prepared from the stock solution. The initial dose was 1/1,000,000 of the therapeutic dose (1/1,000,000 of total dose: 80 mg/1,000,000 = 0.08 μ g). This initial amount of enzyme with 0.05 μ g/ml concentration was calculated as 1.6 ml. The doses were increased by half-log₁₀ (~threefold) increments⁸ every 20–30 min. Therefore, the infusion rates were also increased by threefold every step. However, the concentration was increased every hour. The infusion set contained 25 ml of fluid alone; therefore, 25 ml more was prepared for each concentration (for example, to give 1.6 ml in 30 min, 27 ml was prepared from the stock solution). For the next concentration, the remaining enzyme in the set was thrown and another infusion set was prepared for the consecutive concentration. The infusion rate was reduced to half steps when the patient developed generalised urticaria

in the 9th and 10th steps during the initial two desensitisation weeks. During this time, the infusions were stopped and 2 mg/kg diphenhydramine was given.

After two weeks, no infusion interruption was necessary. During the seventh week, the desensitisation protocol was conducted with the standard dose. Desensitisation was continued every two weeks after the eighth application. The patient received supervised rhGAA treatment for 4.5 months. Thereafter, the Paediatric Metabolism Unit continued to provide rhGAA, based on the protocol shown in Table 2. The patient showed normal growth and normal echo and electrocardiograms, and was able to perform age-appropriate activities at 22 months of age.

Currently there are no safe alternative treatments for PD; therefore, desensitisation is the only option for cases of anaphylaxis in response to rhGAA. The present paper details the only desensitisation protocol available for children in accordance with the general recommended rules.⁹ She is also the youngest patient with PD who is desensitised to rhGAA. To date there are only two published reports of desensitisation to rhGAA, one in an adult patient⁶ and the other in two children⁷ with PD. Although pharmacological desensitisation protocols are increasingly being used, guidelines have not been issued until recently. In 2010, the European Network of Drug Allergy (ENDA) and European Academy of Allergy and Clinical Immunology (EAACI) interest groups on pharmacological hypersensitivity published consensus statements regarding the general considerations for desensitisation for drug hypersensitivity.⁹ In general, protocols should be applied to samples of more than 10 patients.⁹ Therefore, we wanted to use the proposed desensitisation protocol by El-Gharbawy et al.⁷ Even as allergists, however, we found the protocol complex and difficult to understand. The authors did not explain how they calculated the initial dose. Moreover, 10-fold increments were made during the initial steps of the desensitisation protocol. The authors named the steps as micro-dilutions, which they stated that resulted in significant reactions. Desensitisation protocols should rely on general rules and be simple, safe, easy to apply, and modifiable based on the patient's response.^{1,9} The initial dose for desensitisation was determined by taking into account the severity of the reaction. In general, it should be between 1/10,000 and 1/100 of the full therapeutic dose, unless anaphylaxis is severe. In that case, the initial dose should be between 1/1,000,000 and 1/10,000 of the full therapeutic dose.⁹ We preferred a concentration 1/1,000,000 as the initial dose because our patient had a history of severe laryngospasm. Moreover, breakthrough reactions are typically dose dependent and appear more frequently when the increments are excessive. Therefore, it is generally recommended to make two- or threefold increments.^{1,8,9} We chose threefold increments and modified this based on the patient's reaction. The desensitisation procedure was successful in our patient, and the target therapeutic dose was reached with clinical improvement without any significant adverse reactions.

Most patients with PD develop antibodies to ERT, depending upon their CRIM status. The majority of CRIM-positive patients have good therapeutic response to ERT; however, CRIM-negative patients almost consistently do not do well. This may be because they develop high-titre antibodies to rhGAA.¹⁰ Therefore, there is increasing interest in

Table 1 The first desensitisation protocol.

Step	Concentration	Infusion rate (µg/kg/h)	Time (min)	Volume infused per step (ml)	Dose administered with this step (µg)	Cumulative dose (µg)	Fold increase per step
1.	1/100,000	0.02	30	1.6	0.08	0.08	1
2.	1/100,000	0.06	30	4.8	0.24	0.32	3
3.	1/10,000	0.2	30	1.6	0.8	1.12	10
4.	1/10,000	0.6	30	4.8	2.4	3.52	30
5.	1/1000	2	30	1.6	8	11.52	100
6.	1/1000	6	30	4.8	24	35.52	300
7.	1/100	18	30	1.4	72	107.5	1000
8.	1/100	54	30	4.3	216	323.52	3000
9. ^a	1/10	160	30	1.2	648	971.52	10,000
10. ^a	1/10	480	30	3.8	1920	2800	30,000
11.	1/10	750	30	6	3000	5800	45,000
12.	1/1	1500	30	6	5700	11,800	90,000
13.	1/1	3000	60	24	24,000	36,000	180,000
14.	1/1	4000	82	44	44,000	80,000	240,000

Dose: 10 mg/kg/day; the patient's weight: 8 kg; total time: 8 h and 22 min; total volume: 110 ml.

^a The infusion rate was reduced to half steps when the patient developed generalised urticaria in the 9th and 10th steps during the initial 2 desensitisation weeks. Therefore, threefold increments cannot be done. During this time, the infusions were stopped and 2 mg/kg diphenhydramine was given.

immune tolerance induction to ERT in CRIM-negative Pompe patients. Messinger et al.¹¹ treated four CRIM-negative infants with PD patients either therapeutically or prophylactically with rituximab, methotrexate, and/or intravenous gammaglobulin. All patients experienced improvements in motor skills compared with the relentless downhill course of non-tolerant ERT-treated CRIM-negative patients. In another CRIM-negative infant with PD, a monoclonal IgE antibody (omalizumab) was successfully added to ERT after six months of treatment due to a severe IgE-mediated allergic reaction to rhGAA.¹² The authors hypothesised that the anti-IgE antibody used for this patient halted additional allergic reactions and may have played an important role as an immune modulator. In contrast to these two reports, our

patient was a CRIM positive PD patient. Her allergic reaction was a classic severe type I hypersensitivity reaction. In cases of anaphylaxis to medication, the consensus statements of the ENDA and EAACI interest groups recommend desensitisation with a related medication if there is no safe, effective alternative drug treatment.⁹

In conclusion, desensitisation is vital and inevitable for PD patients who develop anaphylaxis to rhGAA. The protocol that we propose here encompasses the general rules of desensitisation: a regimen that is safe, simple, and effective. Although desensitisation procedures have been conducted by different specialists, for the patient's safety, allergists should develop, review, and supervise treatments.

Table 2 The final desensitisation protocol.

Step	Concentration	Infusion rate (µg/kg/h)	Time (min)	Volume infused per step (ml)	Dose administered with this step (µg)	Cumulative dose (µg)	Fold increase per step
1.	1/10,000	0.2	20	1.6	0.85	0.85	1
2.	1/10,000	0.6	20	5	2.5	3.35	3
3.	1/1000	2	20	1.6	8.5	11.8	10
4.	1/1000	6	20	5	26	38	30
5.	1/100	18	20	1.5	77	115	100
6.	1/100	54	20	4.5	230	350	300
7.	1/10	160	20	1.3	680	1000	1000
8.	1/10	500	30	4	2000	3000	3000
9.	1/10	750	30	6.3	3000	6000	4500
10.	1/1	1500	30	6	6000	12,000	9000
11.	1/1	3000	30	13	13,000	25,000	18,000
12.	1/1	5000	20	21	21,000	46,000	30,000
13. ^a	1/1	7000	86	128	128,000	174,000	42,000

Dose: 20 mg/kg/day; the patient's weight: 8.7 kg; stock solution: 5 mg/ml; total time: 6 h and 6 min; total volume: 195 ml.

^a As the patient gained weight requisite doses are added to the final step.

Ethical disclosures

Protection of human subjects and animals in research. The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Patients' data protection. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors have obtained the informed consent of the patient mentioned in the article. The author for correspondence is in possession of this document.

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Drug allergy in haematopoietic stem cell transplantation

To the Editor,

Cutaneous eruptions emerging shortly after haematopoietic stem cell transplantation (HSCT) pose a particular diagnostic challenge for oncologists and consulting dermatologists. Many distinct dermatologic entities occur early in the post-HSCT period, including acute graft-versus-host disease (GVHD), viral exanthema, eruption of lymphocyte recovery, erythema multiforme, toxic erythema of chemotherapy and morbilliform drug eruptions.^{1–3} These diseases are often clinically indistinguishable, and their similar histopathological features may preclude a definitive diagnosis, leading to unfavourable patient outcomes.

Exposure to medications that were previously allergenic to either the stem cell donor or recipient may have implications for the post-transplant course of the HSCT patient.³ The interplay between donor and recipient drug allergy, and its influence on HSCT outcomes has yet to be studied in a systematic manner. It has been suggested that allogeneic HSCT patients can be safely exposed to medications

to which they were previously allergic,⁴ but there are no reports in the literature addressing the consequences of post-HSCT patient exposure to drugs that caused an allergic response in donors. Furthermore, the potential relationship between drug allergy and other cutaneous complications in HSCT patients, such as GVHD, has not been examined.

Our goal was to determine how many post-HSCT patients received medications that they or their donors were allergic to, and characterise any ensuing reactions (cutaneous or otherwise) that occurred. We additionally hypothesized the incidence of acute GVHD to be greater in HSCT recipients that received these medications post-transplant, assuming drug allergy as a contributor to immune activation.

A retrospective chart review was conducted to identify all first-time adult allogeneic HSCT recipients in the Northwestern Memorial Hospital system in 2009. Information collected included demographic and disease-specific information, as well as documented allergies of both stem cell donors and recipients. Medication exposures during the first 60 days post-transplant were recorded and cross-referenced with drug allergies. Incidence and diagnosis of all skin eruptions during this time were also recorded, including acute GVHD.