

may be more common and cause greater concern in DGS because of the PID. Because of limited data in the literature, the mechanisms of effect of biologics in these patients remain to be further studied. We suggest that therapy with TNFis can be effective in patients with JIA and DGS, but frequent regular controls are indispensable for monitoring disease activity and possible side effects of treatment, and for adjusting the therapy.

Mario Sestan, MD*

Nastasia Kifer, MD*

Marijan Frkovic, MD*

Ana-Marija Laskarin†

Marija Jelusic, MD, PhD*

*Department of Paediatrics

University Hospital Centre Zagreb

University of Zagreb School of Medicine

Zagreb, Croatia

†Study of Dental Medicine

Medical Faculty

University of Rijeka

Rijeka, Croatia

marija.jelusic@mef.hr

References

1. Gennery AR, Barge D, O'Sullivan JJ, Flood TJ, Abinun M, Cant AJ. Antibody deficiency and autoimmunity in 22q11.2 deletion syndrome. *Arch Dis Child.* 2002;86:422–425.
2. Sullivan KE, McDonald-McGinn DM, Driscoll DA, et al. Juvenile rheumatoid arthritis-like polyarthritis in chromosome 22q11.2 deletion syndrome (DiGeorge anomalad/velocardiofacial syndrome/conotruncal anomaly face syndrome). *Arthritis Rheum.* 1997;40:430–436.
3. Giancane G, Consolaro A, Lanni S, Davi S, Schiappapietra B, Ravelli A. Juvenile idiopathic arthritis: diagnosis and treatment. *Rheumatol Ther.* 2016;3:187–207.
4. Pelkonen P, Lahdenne P, Lantto R, Honkanen V. Chronic arthritis associated with chromosome deletion 22q11.2 syndrome. *J Rheumatol.* 2002;29:2648–2650.
5. Her M, Kavanaugh A. Alterations in immune function with biologic therapies for autoimmune disease. *J Allergy Clin Immunol.* 2016;137:19–27.
6. Ko JM, Gottlieb AB, Kerbleski JF. Induction and exacerbation of psoriasis with TNF-blockade therapy: a review and analysis of 127 cases. *J Dermatol Treat.* 2009;20:100–108.
7. Brown G, Wang E, Leon A, et al. Tumor necrosis factor- α inhibitor-induced psoriasis: systematic review of clinical features, histopathological findings, and management experience. *J Am Acad Dermatol.* 2017;76:334–341.
8. Thavarajah K, Wu P, Rhew EJ, Yeldandi AK, Kamp DW. Pulmonary complications of tumor necrosis factor-targeted therapy. *Respir Med.* 2009;103:661–669.
9. Uy R, Jacobs N, Mziray-Andrew C. Inflammatory bowel disease and diverticulosis in an adolescent with DiGeorge syndrome. *J Pediatr Gastroenterol Nutr.* 2016;62:e43–e45.
10. Iroh Tam PY, Hanisch BR, Klammer K, DeVries AS. Measles vaccine strain from the skin rash of a DiGeorge patient receiving tumor necrosis factor inhibitor. *Pediatr Infect Dis J.* 2014;33:117.

A 12-steps desensitization protocol for pediatric patients with hypersensitivity to pegylated asparaginase



Asparaginase is a chemotherapeutic used to treat hematologic malignant tumors. Hypersensitivity reactions to native asparaginase (L-asparaginase) are described in up to 60% of patients¹ in whom case switching to alternative forms of asparaginase is recommended: pegylated asparaginase (PEG-asparaginase), a readily available formulation, or *Erwinia*-asparaginase,² which is currently scarce. Although PEG-asparaginase is considered hypoallergenic, up to 25% of patients receiving it have allergic reactions.³ If no additional asparaginase formulations are available, hypersensitivity to PEG-asparaginase is an important cause of drug use discontinuation, which may compromise disease-free survival.⁴ Because of the importance of asparaginase to treat hematologic malignant tumors, desensitization to PEG-asparaginase has been previously attempted, with mixed results.^{5,6}

We prospectively identified pediatric oncology patients with PEG-asparaginase allergy during 2018 and offered them continued administration of the drug through desensitization. This study was approved by the institutional review board, and informed consent was obtained before desensitization.

Five patients with a history of hypersensitivity reactions to PEG-asparaginase, who required additional doses of the medication, were identified. Four patients had acute lymphocytic leukemia, and 1 had lymphoblastic lymphoma. Ages ranged from 2 to 11 years. Two patients who had previously received L-asparaginase reacted to the first dose of PEG-asparaginase, and the remaining 3 patients reacted during their second or third dose of PEG-asparaginase. The severity of the allergic reactions was assessed as previously described⁷; 4 patients had moderate reactions, and 1 had a severe reaction. Symptoms included respiratory distress, angioedema, urticaria, vomiting, and hemodynamic instability that developed within the first 2 hours after PEG-asparaginase administration. During their initial reaction, all patients were treated with intravenous steroids and antihistamines.

All patients received their first PEG-asparaginase desensitization in an intensive care unit (ICU); subsequent desensitizations were performed in the oncology service under continuous cardiovascular and respiratory monitoring and 1-to-1 nursing. Premedications were administered 2 hours before the start of the procedure; all patients received methylprednisolone and montelukast, 2 patients received cetirizine, and 3 received hydroxyzine.

A total of 12 desensitizations to PEG-asparaginase were performed in 5 patients. The protocol consisted of three 100-mL bags with increasing concentrations of PEG-asparaginase (0.25, 2.5, and 25 U/m²/mL) infused for a total of 4.1 hours. The volume of bags 1 and 2 was not completely administered. The total dose of PEG-asparaginase was 2500 U/m² (Table 1).

Three patients underwent desensitization without any breakthrough symptoms. One patient had hives that responded to 0.1 mg/kg of intravenous chlorpheniramine during his first desensitization, after which he did not require subsequent doses of PEG-asparaginase. One additional patient developed hives and vomiting during step 9 that required the procedure to be temporarily stopped. After treatment with 1 mg/kg of intravenous methylprednisolone, 0.1 mg/kg of chlorpheniramine, and 0.15 mg/kg of ondansetron, desensitization was successfully completed. For his 2 subsequent PEG-asparaginase infusions, a 13-step protocol with the same premedication, a maximum infusion rate of 30 mL/h, and a total infusion time of 6 hours was used without any breakthrough symptoms. No patient received epinephrine.

Although the use of desensitization to chemotherapeutics is widely accepted, desensitization to PEG-asparaginase has been less common because of a suitable alternative (*Erwinia*-asparaginase) and concern for hypersensitivity being associated with neutralizing antibodies and reduced biologic activity of the drug.⁸ Despite concern for a link between drug hypersensitivity and development of neutralizing antibodies, up to one-third of patients can have blocking antibodies without presenting with any symptoms of infusion-related reactions, a phenomenon known as silent inactivation,⁹ and a significant proportion of patients treated with PEG-

Disclosures: The authors have no conflicts of interest to report.

Funding: None.

Table 1Example of a PEG-Asparaginase Desensitization Protocol (2500 U/m² of PEG-Asparaginase) for a 0.65-m² Patient^a

Premedication to be administered 2 hours before desensitization					
1. Oral cetirizine (0.3 mg/kg) or oral hydroxyzine (1 mg/kg)					
2. Intravenous methylprednisolone (1 mg/kg)					
3. Oral montelukast (dosing based on age)					
Solution	Total volume, mL	Drug per bag, U		Concentration, U/mL	
1	100	16.25		0.163	
2	100	162.5		1.625	
3	100	1593.03		15.930	
Step	Solution	Rate, mL/h	Time, min	Dose per step, U	Cumulative dose, U
1	1	2	15	0.0813	0.0813
2	1	5	15	0.2031	0.2844
3	1	10	15	0.4063	0.6906
4	1	20	15	0.8125	1.5031
5	2	5	15	2.0313	3.5344
6	2	10	15	4.0625	7.5969
7	2	20	15	8.1250	15.7219
8	2	40	15	16.2500	31.9719
9	3	10	15	39.8257	71.7976
10	3	20	15	79.6514	151.4490
11	3	40	15	159.3028	310.7518
12	3	60	82.5	1314.2482	1625.0000

^aTotal infusion time was 247.5 minutes.

asparaginase develop antibodies without compromising the drug's biological activity or showing signs of allergic reactions.⁹

Current guidelines on the management of patients with allergic reactions to PEG-asparaginase recommend switching to *Erwinia*-asparaginase or continuing with PEG-asparaginase according to the severity of the patient's reaction and enzymatic activity.² However, in countries where *Erwinia*-asparaginase and measurement of asparaginase activity are not available, use of the drug must be discontinued.⁴ Because this may affect disease-free survival of patients and *Erwinia*-asparaginase is not available in Chile, we opted for PEG-asparaginase desensitization in these patients. To date, only 2 desensitization protocols for PEG-asparaginase have been published.^{5,6} The protocol reported by Sahiner et al⁵ was unsuccessful because the 2 patients in their study developed anaphylaxis during desensitization. The use of higher infusion rates, more concentrated initial solutions, a 32-fold increase in concentration between solutions, and a shorter total infusion time may explain their high incidence of anaphylaxis. Most recently, Verma et al⁶ reported a 13-step desensitization protocol with a total infusion time of 6 hours using the 3-bag method. Of 10 patients in the report by Verma et al,⁶ 8 were successfully desensitized, whereas 2 developed hypersensitivity reactions reported as mild that required epinephrine. All procedures in the report by Verma et al⁶ were performed in the ICU, and premedication consisted of diphenhydramine and hydroxyzine as well as ranitidine and famotidine with or without steroids and montelukast. In addition, Verma et al⁶ reported that enzymatic activity after desensitization was maintained above therapeutic range in 8 of 10 patients after 4 to 7 days and in 7 of 10 patients after 10 to 14 days. Because enzymatic activity was compromised in a few desensitized patients, the report by Verma et al⁶ provides additional evidence in favor of desensitization in patients with PEG-asparaginase hypersensitivity in settings where *Erwinia*-asparaginase is not available.

We report a successful 12-step desensitization protocol to PEG-asparaginase used in pediatric patients. Although our protocol is similar to the one reported by Verma et al,⁶ ours was safely used in the oncology service after patients had a successful desensitization in the ICU, is shorter, and includes montelukast instead of a histamine₂-blocker as premedication. We opted to systematically use montelukast instead of ranitidine and famotidine because

premedication in the unsuccessful protocol reported by Sahiner et al⁵ consisted of methylprednisolone, hydroxyzine, and ranitidine, and the use of montelukast in premedication regimens has been reported to decrease the severity of hypersensitivity reactions during desensitization.¹⁰ Contrary to a previous report,⁵ the experience using desensitization in patients with PEG-asparaginase allergy presented here, and previously by Verma et al,⁶ suggests that it is a feasible and safe alternative to drug treatment discontinuation that might benefit pediatric patients with hematologic malignant tumors. Further longitudinal studies are needed to evaluate whether the systematic use of PEG-asparaginase desensitization improves long-term outcomes in patients with PEG-asparaginase hypersensitivity in the absence of *Erwinia*-asparaginase.

S. Concha, MD*

F. Barriga, MD†

P. Ovalle, MD‡

R. Hoyos-Bachiloglu, MD, MMSc*

*Department of Pediatric Infectious Diseases and Immunology School of Medicine

Pontificia Universidad Católica de Chile

Santiago, Chile

†Pediatric Hematology and Oncology Section

School of Medicine

Pontificia Universidad Católica de Chile

Santiago, Chile

‡Pediatric Oncology Unit

Hospital Sótero del Río

Servicio de Salud Metropolitano Sur-Oriente

Santiago, Chile

rahoyos@puc.cl

References

1. Rau RE, Dreyer Z, Choi MR, et al. Outcome of pediatric patients with acute lymphoblastic leukemia/lymphoblastic lymphoma with hypersensitivity to pegasparaginase treated with PEGylated *Erwinia* asparaginase, pegcrisantas-pase: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2018; 65(3): e26873.

2. van der Sluis IM, Vrooman LM, Pieters R, et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. *Haematologica*. 2016;101(3):279.
3. Burke Michael J, Devidas Meenakshi, Maloney Kelly, et al. Severe peg-asparaginase hypersensitivity reaction rates (grade ≥ 3) with intravenous infusion vs. intramuscular injection: analysis of 54,280 doses administered to 16,534 patients on children's oncology group (COG) clinical trials. *Leuk Lymphoma*. 2018;59(7):1624–1633.
4. Kyonen M, Folatre I, Zolezzi P, et al. Adverse reactions to l-asparaginase in children with acute lymphatic leukemia. *Rev Méd Chile*. 2006;134:1530–1534.
5. Sahiner UM, Yavuz ST, Gökce M. Anaphylactic reaction to polyethylene-glycol conjugated-asparaginase: premedication and desensitization may not be sufficient. *Pediatr Int*. 2013;55(4):531–533.
6. Verma A, Chen K, Bender C, Gorney N, Leonard W, Barnette P. PEGylated *E. coli* asparaginase desensitization: an effective and feasible option for pediatric patients with acute lymphoblastic leukemia who have developed hypersensitivity to pegaspargase in the absence of asparaginase *Erwinia chrysanthemi* availability. *Pediatr Hematol Oncol*. 2019;36(5):277–286.
7. Brown S. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol*. 2004;114:371–376.
8. Panosyan EH, Seibel NL, Martin-Aragon S, et al. Asparaginase antibody and asparaginase activity in children with higher-risk acute lymphoblastic leukemia: Children's Cancer Group Study CCG-1961. *J Pediatr Hematol Oncol*. 2004;26(4):217–226.
9. Tong W, Pieters R, Tissing W, van der Sluis I. Desensitization protocol should not be used in acute lymphoblastic leukemia patients with silent inactivation of PEGasparaginase. *Haematologica*. 2014;99(7):e102–e104.
10. Breslow R, Caiado J, Castells M. Acetylsalicylic acid and montelukast block mast cell mediator-related symptoms during rapid desensitization. *Ann Allergy Asthma Immunol*. 2009;102(2):155–160.

A case of cutaneous *Mycobacterium chelonae* in common variable immunodeficiency



Mycobacterium chelonae is a rare acid-fast bacillus that grows rapidly when compared with other members of the *Mycobacteria* genus. Localized cutaneous infections (ie, cellulitis and abscess) are common in immunocompetent patients, but in an immune compromised host disseminated infections are more prevalent. Disseminated cutaneous manifestations most commonly present in patients who are immunosuppressed by malignant neoplasms, corticosteroid therapy, and various immunomodulating drugs used in organ transplantation or secondary immunodeficiencies.¹ However, no cases have been reported in association with primary immunodeficiencies, such as common variable immunodeficiency (CVID). CVID is characterized by a failure of B-cell differentiation that causes defective immunoglobulin production.² We describe the first case, to our knowledge, of cutaneous *M chelonae* associated with CVID.

The patient is a 39-year-old woman with a medical history of CVID, adrenal insufficiency, and mixed connective tissue disease. She was initially diagnosed with CVID in 2010 and has been receiving weekly subcutaneous intravenous immunoglobulin injections (Cuvitru). She later developed a severe cough, fevers, and productive sputum and was diagnosed with *Mycobacterium avium* complex via bronchoscopy and received 18 months of antimicrobial treatment. The patient was subsequently prescribed suppressive azithromycin therapy.

The patient then began to develop multiple erythematous, itchy, and painful nodules and plaques on her bilateral lower extremities. The nodules initially started on her legs but then spread to her forearms and hands (Fig 1). The patient had intermittent fevers and chills, dysphagia, and an associated 50-lb weight loss. An initial punch biopsy specimen was obtained of 2 representative lesions on her right medial proximal leg and right ventral proximal forearm, and both revealed cutaneous bacterial infection with acid-fast bacilli and gram-variable bacilli. The laboratory values at the time were significant for a CD3 absolute count of 642/ μ L, CD4 absolute count of 385/ μ L, and CD8 absolute count of 223/ μ L. Additional biopsy specimens were obtained for bacterial and fungal cultures, which resulted in mycobacterial tissue culture positive for *M chelonae*. She underwent genetic testing, the results of which were negative for 300 primary immunodeficiencies. Interestingly, the results were positive for a *CSF2RA* mutation. This mutation is associated with autosomal recessive primary pulmonary alveolar proteinosis, but the clinical significance of this remains unclear.

Mycobacterium is a genus of *Actinobacteria*, with more than 190 recognized species. This genus is best known for pathogens that

cause diseases such as tuberculosis and leprosy. *M chelonae* was first described in 1903 after being isolated from a turtle. It is a nonmotile, non-spore-forming, gram-positive, acid-fast bacillus, which is a nontuberculous, rapidly growing mycobacterium found throughout the environment, including soil, water, and aquatic animals. It is one of the most pathogenic, rapidly growing mycobacteria and is associated with skin infections, catheter, or post-surgical infections, with invasive infections being more common in immunosuppressed patients, including those with HIV infection, transplant suppression, and long-term steroid use.³ However, little has been described concerning the association of primary immunodeficiencies and *M chelonae*.

CVID is a primary immunodeficiency that presents in affected individuals as a susceptibility to recurrent infection with encapsulated organisms and an increased propensity to develop inflammatory and/or autoimmune manifestations. CVID is characterized by a failure of B-cell differentiation, causing defective immunoglobulin production.⁴ Recent emerging data suggest a T-cell component of CVID marked by premature arrest in thymic output, leading to T-cell exhaustion and immune dysregulation. CD4 T-cell lymphopenia was first noted among patients with CVID and can markedly reverse the normal CD4/CD8 ratio when combined with expansion of senescent CD8 T cells, a feature not usually found in other antibody deficiencies.⁵ This aberrancy of the T-cell compartment may lead to infections by opportunistic organisms. We describe the first case, to our



Figure 1. Left forearm.