JPPT | Case Report

A 12-Step Desensitization Protocol for Calaspargase Pegol-mknl

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Asparaginase is a standard treatment for acute lymphoblastic leukemia (ALL) of childhood. As a bacteria-derived enzyme, asparaginase is highly immunogenic, and hypersensitivity reactions (HSRs) routinely lead to drug discontinuation. HSRs remain common even with the introduction of pegaspargase, a PEGylated version of *Escherichia coli*-derived asparaginase. Asparaginase *Erwinia chrysanthemi* (recombinant)-rywn (recombinant Erwinia) is an alternative for those with HSRs to pegaspargase. Here, we describe an 11-year-old boy with relapsed ALL who developed HSRs to both pegaspargase and recombinant Erwinia. This is the report of a novel desensitization protocol for calaspargase pegol-mknl (calaspargase) with no adverse events and adequate serum asparaginase activity.

ABBREVIATIONS AE, adverse event; ALL, acute lymphoblastic leukemia; BMI, body mass index; calaspargase, calaspargase pegol-mknl; COG, Children's Oncology Group; CTCAE 5.0, Common Terminology Criteria for Adverse Events version 5; FDA, Food and Drug Administration; HSRs, hypersensitivity reactions; IM, intramuscular; IV, intravenous; PO, oral; recombinant Erwinia, Asparaginase *Erwinia chrysanthemi* (recombinant)-rywn; SAA, serum asparaginase activity

KEYWORDS asparaginase; calaspargase; desensitization protocol; hypersensitivity; leukemia

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Introduction

Asparaginase is essential for the treatment of childhood acute lymphoblastic leukemia (ALL). By depleting asparagine, a key source of growth for malignant hematopoietic cells, asparaginase can induce leukemic cell death.[1] However, as a bacterial enzyme, asparaginase is highly immunogenic and often triggers hypersensitivity reactions (HSRs), leading to subsequent drug discontinuation. Despite the introduction of pegaspargase, a PEGylated version of *Escherichia coli*-derived asparaginase, HSRs remain a common adverse event (AE).[1] The incidence of HSRs to pegaspargase has been reported to be 3% to 24%.[1] In patients with HSRs to pegaspargase, asparaginase *Erwinia chrysanthemi* (recombinant)-rywn (recombinant Erwinia) can serve as an alternative form of asparaginase, as it is antigenically distinct.[2] Despite utilizing this alternative form of asparaginase, the incidence of HSRs to recombinant Erwinia have been reported to be 25%.[1] Here, we describe an 11-year-old boy with relapsed ALL who experienced HSRs to both pegaspargase and recombinant Erwinia. With the goal to safely provide asparaginase therapy, he underwent a novel 12-step desensitization protocol with calaspargase pegol-mknl (calaspargase), a second-generation PEGylated *E coli*-derived asparaginase product. This report highlights a safe and effective desensitization protocol for calaspargase with no AEs and therapeutic serum asparaginase activity (SAA).

Case Report

A 10-year-old boy weighing 70 kg presented with pallor and evaluation revealed leukocytosis, anemia, and thrombocytopenia. Bone marrow examination confirmed pre-B ALL. Chemotherapy was started according to the Children's Oncology Group (COG) protocol AALL1732. The patient received 1 dose of pegaspargase 4325 units (2500 units/m^2/dose) on day 4 of induction and a second dose of pegaspargase 3750 units (2142 units/m^2/dose) on day 15 of consolidation therapy. The second dose of pegaspargase at a lower amount aligned with COG mandates that all high-risk ALL patients under 20 years of age with a body mass index (BMI) exceeding the 95th percentile have their pegaspargase dose capped at 3750 units. All pegaspargase doses were diluted in 100 mL of normal saline, infused intravenously (IV) over 2 hours, and concurrently with normal saline at 50 mL/hr. The patient also received pre-medications including diphenhydramine (1 mg/kg/dose IV/PO, maximum 50 mg/dose), ondansetron (0.15 mg/kg/dose IV/PO, maximum 8 mg/dose), and famotidine (0.5 mg/kg/dose IV/PO, maximum 20 mg/dose) 30 to

60 minutes prior to infusion. No SAA concentrations were collected.

On day 43 of consolidation, the patient received his third dose of pegaspargase, capped at 3750 units (2094 units/m^2/dose). Seven minutes into the infusion, he developed pruritus and diffuse urticaria from head to toe. Urticaria remained despite IV diphenhydramine 50 mg and hydrocortisone 100 mg. He vomited and became hypotensive (blood pressure of 70/54 mm Hg), which prompted administration of intramuscular (IM) epinephrine 0.3 mg. Due to not completing the entire pegaspargase infusion, SAA concentrations were not collected. His symptoms were consistent with a grade 3 AE according to the Common Terminology Criteria for Adverse Events version 5 (CTCAE 5.0) from the National Cancer Institute.[3] Therefore, in accordance with the AALL1732 study, each dose of pegaspargase was replaced with 6 doses of IM recombinant Erwinia according to a schedule of 25 mg/m^2/dose on Mondays and Wednesdays, and 50 mg/m^2/dose on Fridays. Per institutional standards, no pre-medications were given prior to any dose of recombinant Erwinia, and no SAA concentrations were collected. The patient completed 4 rounds of recombinant Erwinia IM injections (6 doses each round). However, during the fifth round, approximately 15 hours after the fourth dose, the patient developed diffuse urticaria involving arms and legs. Oral diphenhydramine (50 mg/dose) every 6 hours only provided temporary relief. He returned to the hospital 36 hours after and received IV diphenhydramine 50 mg and hydrocortisone 100 mg. Within 2 hours, the urticaria returned. Finally, IV methylprednisolone 80 mg and PO cetirizine 10 mg resolved the urticaria. There were no other symptoms reported. The urticaria was classified as a grade 2 AE (CTCAE 5.0). No SAA concentrations or blood ammonia concentrations were collected. His extensive medication list was reviewed. No other potential triggers were identified. The remaining recombinant Erwinia doses were omitted.

Thirteen months after the initial diagnosis, the patient, now 11 years old, relapsed. He was admitted for re-induction chemotherapy per COG protocol AALL1331. Pegaspargase was indicated in the relapsed chemotherapy regimen, however calaspargase was the only available PEGylated asparaginase product due to product availability restrictions implemented by the drug manufacturer in December 2022.[1,4] Therefore, a desensitization protocol for calaspargase was created to ensure safe administration of the medication (Table 1). The decision was made to include overfill in each bag to facilitate closed medication system priming of the infusion line on the nursing unit and minimize infusion interruptions when transitioning between bags. Each bag of calaspargase was stored at refrigerated

Table 1. Intravenous Desensitization Protocol for calaspargase pegol-mknl

	Volume (mL)	Concentration (units/mL)	Units/Bag
Bag A	150	0.05	7.5
Bag B	105	0.5	52.5
Bag C	375	10	3750

Step	Bag	Concentration (Units/mL)	Rate (mL/hr)	Infusion Time (min)	Administered Dose (mL)	Administered Dose (units)	Cumulative Dose (units)
1	A	0.05	10	15	2.5	0.125	0.125
2	A	0.05	20	15	5	0.25	0.375
3	A	0.05	40	15	10	0.5	0.875
4	A	0.05	80	15	20	1	1.875
5	B	0.5	20	15	5	2.5	4.375
6	B	0.5	40	15	10	5	9.375
7	B	0.5	80	15	20	10	19.375
8	B	0.5	160	15	40	20	39.375
9	C	10	15	15	3.75	37.5	76.875
10	C	10	30	15	7.5	75	151.875
11	C	10	60	15	15	150	301.875
12	C	10	120	172	344	3440	3741.875

temperatures, assigned a beyond use date of 24 hours in accordance with manufacturer recommendations, and dispensed immediately prior to initiation.

The patient was admitted to the pediatric intensive care unit and assigned one-to-one nursing care. Baseline measurements included weight of 88.6 kg, height of 161 cm, and body surface area of 1.99 m^2. A pre-infusion serum tryptase concentration was normal at 2 mcg/L (<11 mcg/L). The patient received pre-medications including oral cetirizine 10 mg, montelukast 5 mg, oral famotidine 20 mg (2 hours prior to the desensitization) and IV methylprednisolone 80 mg (1 hour prior to desensitization). During the infusion, normal saline was concurrently infused at a rate of 50 mL/hr. He was prescribed 3750 units of calaspargase (1884 units/m^2/dose) due to dose capping in patients with a BMI above the 95th percentile. Considering logistical challenges associated with the selected desensitization approach and limitations of the infusion pump, a total of 3741 units was administered. Bag A was infused for 60 minutes, bag B for 60 minutes, and bag C for 217 minutes, for a total infusion time of 337 minutes. All bags were utilized within the 24-hour refrigerated beyond use date and each bag was exposed to room temperature for less than 4 hours, thereby adhering to USP <797> sterility guidelines and manufacturer stability guidelines. Vital signs were monitored every 15 minutes for the first hour, then every 30 minutes until 2 hours after completion of the infusion. No AEs were reported. Institutional standards for monitoring PEGylated asparaginase were developed (Table 2) based on a previously published study as well as COG guidance.[5] The SAA concentration 7 days post-calaspargase infusion was 1.052 IU/mL, meeting the institutional SAA goal of above 0.4 IU/mL and negating the need to draw further SAA concentrations.

Table 2. PEGylated Asparaginase Monitoring Standards (pegaspargase/calaspargase)

Obtain serum L-asparaginase activity (SAA) assay 7 +/− 3 days after each full dose of PEGylated asparaginase administration.
Interpretation of results: • < 0.1 IU/mL ➔ switch to recombinant Erwinia (silent inactivator) • 0.1–0.4 IU/mL ➔ per clinician discretion; consider obtaining another L-asparaginase activity level at 14 days after initial infusion with goal concentration ≥ 0.1 IU/mL • > 0.4 IU/mL ➔ continue PEGylated asparaginase (therapeutic)

Discussion

The discovery of asparaginase for treating childhood leukemia dates back to 1953.[6] The first commercially available *E coli*-derived asparaginase product, native L-asparaginase, was approved by the US Food and Drug Administration (FDA) in 1978. Although asparaginase therapy was associated with improved overall survival rates, patients had frequent HSRs, manifested by localized erythema/urticaria to systemic anaphylaxis.[1,4,6–9] To reduce immunogenicity and extend the half-life of asparaginase, a polyethylene glycol (PEG) moiety was added in 1994, thus creating a second formulation of asparaginase, pegaspargase.[8] In 2011, a third asparaginase formulation, asparaginase Erwinia chrysanthemi, which was an *Erwinia chrysanthemi*-derived asparaginase product, became available and was less immunogenic.[2,9–11] Unfortunately, asparaginase Erwinia chrysanthemi was plagued with persistent drug shortage issues. Therefore, in 2021, a fourth asparaginase formulation, asparaginase *Erwinia chrysanthemi* (recombinant)-rywn (recombinant Erwinia), was introduced and replaced asparaginase Erwinia chrysanthemi. Recombinant Erwinia must be administered in multiple doses (6:1 ratio) to achieve the tumor effectiveness of a single IV dose of pegaspargase. A landmark study in 2020 demonstrated that high-risk ALL pediatric patients who discontinue asparaginase early due to HSRs or other toxicity have an inferior disease-free survival compared with those receiving all prescribed doses.[12] In turn, desensitization is a favorable option for allowing administration of recommended asparaginase doses and may be the most practical, cost-effective approach.[13]

This case report describes a patient who experienced AEs to both pegaspargase and recombinant Erwinia. To ascertain if a desensitization procedure was necessary, we first sought to rule out an infusion-related reaction. This type of drug reaction is not antibody-mediated, but its presenting symptoms can overlap with those of HSRs.[10,11] Infusion-related reactions can occur following initial exposure to an agent; in contrast, HSRs require repeated exposure to promote antibody development. Symptoms such as fever, hypertension, throbbing headache, incontinence, or pelvic pain can be seen in infusion-related reactions but are uncommon in HSRs.[10] Based upon the timing and characteristics of his signs and symptoms, the allergy-immunology service concluded that the clinical presentation was more consistent with HSRs.

Given our patient's history of adverse reactions to both pegaspargase and recombinant Erwinia and the lack of availability of pegaspargase due to manufacturer restrictions imposed as of December 2022, combined with the necessity for asparaginase in relapsed chemotherapy regimens, we elected to develop a desensitization protocol for calaspargase. Approved by the FDA in 2018, calaspargase, a fifth asparaginase formulation, is used in the treatment of de novo and relapsed ALL in children and adolescents between 31 days and

21.5 years of age.[1,4] Similar to pegaspargase, calaspargase is PEGylated, but by adapting a more stable succinimidyl carbonate linker, calaspargase has a longer half-life.[14] Although our patient had never received calaspargase, it was assumed that any potential anti-pegaspargase or anti-asparaginase antibodies developed from his previous HSR to pegaspargase and recombinant Erwinia could interfere with calaspargase.[15,16] Preclinical studies suggest that calaspargase and pegaspargase share similar pharmacodynamic properties, toxicity profiles, drug moieties, and *E coli* derivation.[14,17] Temporary induction of tolerance to pegaspargase through incremental desensitization regimens have been reported previously.[18–22] We postulated that a desensitization protocol to pegaspargase would also be effective for calaspargase. We selected a protocol with a longer infusion period to minimize the risk of an HSR.[20]

Prior to the desensitization protocol, a serum tryptase concentration was obtained and was within normal limits. A transient elevation in serum tryptase with immunoglobulin E-mediated symptoms supports the diagnosis of anaphylaxis.[1,21,23] Since our patient tolerated the calaspargase infusion, a second serum tryptase concentration was not collected. Additionally, silent inactivation of asparaginase is a known complication of asparaginase therapy. In such instances, antibodies form without causing overt clinical symptoms, leading to the inactivation of asparaginase and rendering chemotherapy ineffective.[1,7,9] Therefore, SAA monitoring after infusion of a PEGylated asparaginase product is recommended to identify the presence of silent inactivation and assess clinical efficacy.[1] Since the timing of SAA monitoring has not been standardized, our institution developed its own PEGylated asparaginase monitoring standards (Table 2) based on current literature and COG recommendations. The target SAA must be at least 0.4 IU/mL 4 to 10 days after pegaspargase administration.[5] If SAA is 0.1 to 0.4 IU/mL 4 to 10 days post-infusion, a second SAA would be obtained at day 14 post-infusion with a target of >0.1 IU/mL.[1,5] With asparaginase having a longer depletion time and the minimum accepted SAA value of > 0.1 IU/mL at day 14, we applied the level initially created for pegaspargase to calaspargase.[1,5] One week post calaspargase infusion, SAA in our patient was 1.052 IU/mL, negating the need for additional SAA concentrations and thus proving to be a successful desensitization protocol for calaspargase.

Several months after this case, we utilized our calaspargase desensitization protocol again for another pediatric patient with relapsed ALL and HSRs to pegaspargase. This second patient had a similarly successful outcome with no AEs and detectable SAA on day 7 (1.615 IU/mL) and day 14 (0.685 IU/mL) post-infusion.

This case report does have some limitations. The patient's late reaction to recombinant Erwinia raises the possibility that our patient may not have had a true HSR to recombinant Erwinia. There is a paucity of literature categorizing HSRs toward recombinant Erwinia. Furthermore, a desensitization protocol for intramuscular medication is not a standard practice. There are also no anti-asparaginase, anti-pegaspargase antibody, and SAA concentration during the first diagnosis/upfront leukemia treatment regimen. It was not standard practice to obtain SAA concentrations when this patient initially presented with leukemia. Lastly, there is no universal consensus about the optimal timing for SAA concentrations; some institutions monitor on days 3 to 7, others on day 14, and still other sites use day 21 post infusion as their benchmark.[7,9]

Conclusions

Asparaginase-based therapies remain a cornerstone treatment for pediatric ALL. Calaspargase is a recently approved PEGylated, *E coli*-derived asparaginase product with a longer half-life and similar side effect profile compared to pegaspargase. We report a 12-step desensitization protocol to calaspargase, that was well-tolerated by a patient with HSRs to both pegaspargase and recombinant Erwinia. As calaspargase becomes more widely utilized, this protocol will be useful for clinicians.

Article Information

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution. However, given the nature of this case report, informed consent was not required by our institution.

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