

Tolerability and Efficacy of a 1-Bag Pegaspargase Desensitization Protocol in Pediatric Oncology Patients

Jesse Cramer, PharmD, Justin Graff, PharmD, and David Serebin, BS Pharm

Summary: Desensitization to pegaspargase has been previously attempted in patients who have a hypersensitivity reaction to pegaspargase when Erwinia asparaginase is not an available alternative because of supply issues. Often, these desensitizations have utilized a 3-bag method to complete the infusion. Retrospective chart review was utilized to evaluate the tolerability and efficacy of a 1-bag method for pegaspargase desensitization at a single center. Pegaspargase was infused over ~3 hours with increases to the infusion rate every 15 minutes. Fifteen pediatric patients received a total of 28 pegaspargase infusions utilizing a 1-bag method. In total, 23 of the infusions were able to be successfully completed without signs of hypersensitivity reactions. In addition, 9 of the 15 patients were able to both successfully complete all infusions during the study period and have asparaginase levels within the therapeutic range 7 to 14 days after the infusion. Four of the 5 patients that did experience a hypersensitivity reaction were able to complete the infusion, however, none of these patients had acceptable asparaginase levels postinfusion. No patient required intubation or advanced life support measures secondary to anaphylaxis. Overall, the pegaspargase method described here was successful and well tolerated in a majority of patients.

Key Words: asparaginase, pediatric, leukemia, infusion reactions, desensitization

(*J Pediatr Hematol Oncol* 2021;00:000–000)

Pediatric acute lymphoblastic leukemia and lymphoblastic lymphoma utilize asparaginase therapy as part of standard treatment protocols. Successful completion of asparaginase therapy is vital to maximizing survival outcomes.¹ In the United States, there are 3 available asparaginase products: pegaspargase, Erwinia asparaginase, and calaspargase.² Pegaspargase is the preferred asparaginase product for reducing asparagine availability to leukemia cells because of requiring fewer administrations and incurring less cost than treatment with *Escherichia coli* asparaginase.³ Pegaspargase is the pegylated form of *E. coli* asparaginase. A subset of patients treated with pegaspargase will have hypersensitivity reactions or silent inactivation of the medication, necessitating a shift to Erwinia asparaginase to complete therapy.⁴ Hypersensitivity occurs in ~10% to 25% of patients receiving pegaspargase.^{5,6} Erwinia asparaginase is derived from *Erwinia chrysanthemi*, which offers a different antigen in the event of pegaspargase hypersensitivity reactions.^{7,8} In late 2018, Erwinia asparaginase supply in the United States became erratic, leaving lymphoblastic leukemia and lymphoblastic lymphoma patients

without a core therapeutic option when an allergic reaction occurred from pegaspargase administration.⁹ When asparaginase therapy is reduced or omitted from treatment, outcomes in those patients are poor.^{7,10} In an effort to safely continue asparaginase therapy in patients who had reacted to an infusion of pegaspargase, some institutions attempted a slower “desensitization” infusion of pegaspargase. This could involve three different dilutions of pegaspargase administered over an extended time period in an effort to minimize hypersensitivity reactions.^{7,8,10,11} An alternative to the previously published 3-bag method is a 1-bag method that was created as an adaptation of the 3-bag method. The 1-bag method reduces the complexity for provider ordering, pharmacy preparation, and nursing administration. A retrospective review was undertaken to evaluate the efficacy of this 1-bag pegaspargase (hereafter referred as 1-bag PEG) desensitization protocol.

MATERIALS AND METHODS

Retrospective chart review was utilized to identify patients who previously had a documented hypersensitivity reaction to standard pegaspargase administration and then received a 1-bag PEG desensitization between January 1, 2019 and May 31, 2020. All identified patients were included, even if the desensitization infusion was not completed because of adverse reactions. There were no exclusion criteria. Patient data collected included demographic information, cell line lineage of lymphoblastic leukemia or lymphoblastic lymphoma, and number of standard pegaspargase infusions previously tolerated. Infusion details of 1-bag PEG desensitization collected included prophylactic medications administered before desensitization attempt, dose of pegaspargase, concentration of infused pegaspargase, infusion time, documented adverse reaction(s) to infusion, rescue medications administered during the infusion secondary to presumed hypersensitivity reaction, and asparaginase levels obtained after the infusion. Prophylactic medication timing was also collected to assess if the medications were given within 75 minutes of pegaspargase infusion starting. A patient was considered to have a hypersensitivity reaction if there was documentation in a provider or nursing progress note in the electronic medical record stating that an infusion reaction, hypersensitivity reaction, or allergic reaction occurred, the infusion was paused or stopped, rate of infusion decreased, or rescue medication administered during the infusion. Rescue medications included histamine receptor type 1 or histamine receptor type 2 antagonists, intravenous steroids, and intramuscular or intravenous epinephrine. All patients receiving the 1-bag PEG desensitization were monitored in the intensive care unit for signs of serious allergic reactions. Allergic reactions, when they occurred, were managed at the discretion of the intensive care unit provider and bedside

Received for publication February 23, 2021; accepted May 20, 2021.
From the Children's Wisconsin, Milwaukee, WI.

The authors declare no conflict of interest.

Reprints: Jesse Cramer, PharmD, Children's Wisconsin, P.O. Box 1997,
MS 730, Milwaukee, WI 53201 (e-mail: jlcramer@chw.org).

Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 1. Example Infusion Chart

Concentration (units/mL)	Rate (mL/h)	Minutes	Dose Infused per Step (units)	Cumulative Dose (units)	Volume Infused per Step (mL)	Cumulative Volume (mL)
2.1	0.57	15	0.30	0.30	0.14	0.14
2.1	1.14	15	0.60	0.90	0.29	0.43
2.1	2.38	15	1.25	2.15	0.60	1.02
2.1	4.76	15	2.50	4.65	1.19	2.21
2.1	11.43	15	6.00	10.65	2.86	5.07
2.1	23.81	15	12.50	23.15	5.95	11.02
2.1	47.62	15	25.00	48.15	11.90	22.93
2.1	95.24	15	50.00	98.15	23.81	46.74
2.1	238.10	15	125.00	223.15	59.52	106.26
2.1	476.19	15	250.00	473.15	119.05	225.31
2.1	952.38	15	500.00	973.15	238.10	463.40
2.1	977.95	~30 min until full volume has been infused	1026.85	2000.00	488.98	952.38

Ordered dose = 2000 units.

Concentration (units/mL) = 2.1 units/mL.

nurse. Grading of allergic reactions was completed according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE).¹²

The 1-bag PEG solution was prepared in a single IV-bag with primed tubing and stored refrigerated before administration. The concentration prepared was unique to each patient and was selected by the pharmacist so that it would allow for the first step of the desensitization to deliver 0.015% of the total dose at a rate of at least 0.1 mL/h. This is the lowest achievable rate for the infusion devices that were utilized. Each subsequent rate increase delivered approximately twice the dose delivered in the previous step, up to a maximum infusion rate of 999 mL/h (Table 1). A Microsoft Excel (Microsoft Corporation, Redmond, WA) worksheet was created to aid the pharmacist in the calculation of the final concentration and infusion rates for each step. If the rate titration calculation for the final titration step was calculated out to >999 mL/h, the infusion was capped at 999 mL/h which is the maximum rate that the infusion device would allow. To provide more laminar medication flow through the intravenous line during the first 4 titration steps, all patients received 0.9% sodium chloride infused at the Y-site at 5 mL/h. Before initiating the infusion, all patients received intravenous or oral steroids, intravenous diphenhydramine, oral cetirizine, and oral montelukast ~30 to 60 minutes before start of the infusion. Rescue medications were also readily available in case of hypersensitivity reaction.

The primary outcome measure was the percentage of infusions that were able to be successfully completed without documentation of any signs of hypersensitivity reaction or the need for rescue medications to be administered. The secondary outcome measure was the percentage of patients who both tolerated all 1-bag PEG infusions administered and had acceptable asparaginase levels (>0.1 IU/mL) collected within 14 days of the infusion. While no official cut-offs for acceptable asparaginase levels are recommended, levels of >0.1 IU/mL at 7 to 14 days postinfusion have been used as a marker of efficacy.¹³ Asparaginase activity levels were quantified by a laboratory utilizing a spectrophotometry-based enzyme-coupled reaction. Because of the small number of patients, descriptive statistics were used to analyze the data. Consent for this retrospective study was obtained from the institutional review board.

RESULTS

Retrospective chart review identified a total of 15 patients who had the 1-bag PEG desensitization administered during the study period. These 15 patients received a total of 28 infusions. Demographic information can be seen in Table 2. Before having a documented reaction to standard administration of pegaspargase, all patients identified had tolerated between 1 and 3 standard pegaspargase infusions. All standard administrations of pegaspargase were premedicated with both an H₁ and H₂ receptor antagonist. Twelve of the 15 patients were administered the 1-bag PEG infusion within 30 days of their hypersensitivity reaction to a standard pegaspargase infusion (median 7 d, range: 2 to 1275 d). Reactions to the standard pegaspargase infusion were all documented in the electronic medical record as grade 3 or grade 4 based on CTCAE criteria. Hypotension, flushing, and hives were among the most commonly reported symptoms of the hypersensitivity reactions to the standard pegaspargase infusion. All patients received steroids, intravenous diphenhydramine, oral cetirizine, and oral montelukast before the 1-bag PEG desensitization. The steroid used before the infusion was intravenous methylprednisolone or an equivalent dose of oral prednisone. One patient received intravenous hydrocortisone. However, the premedications were only given within 75 minutes of 1-bag PEG initiation in 20 of the 28 infusions. The remaining 8 infusions had the premedications administered between 76 and 180 minutes before the infusion.

All infusions had planned rate titrations every 15 minutes which resulted in a planned infusion time of ~195 minutes, as described above in the methods section and Table 1. Final concentration of the prepared pegaspargase solution ranged from 1.95 to 6.4 units/mL. The total volume of the infusions ranged from 500 to 1000 mL based on the size of the patient and appropriate pegaspargase dilutions as previously described. Twenty-seven of the 28 infusions were ordered at a dose of 2500 units/m²; the lone exception was a dose of 1000 units/m².

Of the 28 infusions administered, 27 were able to be completed. The median infusion time was 212 minutes (interquartile range: 206 to 225 min). In total, 23 of the 28 infusions (82%) were completed successfully without any signs of hypersensitivity reactions. Five infusions (5 separate

TABLE 2. Patient Characteristics and Pegaspargase Infusion Outcomes

Patient	Patient Age at Time of First 1-bag PEG Administration (y)	Ethnicity	Oncologic Diagnosis	Standard PEGaspargase Infusions Tolerated Before Having an Infusion Reaction	BSA at Time of First 1-Bag PEG Desensitization	Number of 1-Bag PEG Desensitizations Administered During the Study Timeframe	Documented Infusion Reaction Grade*	Asparaginase Activity Level (IU/mL) (1-Bag PEG Infusion #)†
1	10	Hispanic or Latino	B-cell ALL	2	1.32	2	None	(1) Not drawn (2) 0.659
2	8	Caucasian	B-cell ALL	1	1.24	3	None	(1) Not drawn (2) 1.074 (3) Not drawn
3‡	10	Caucasian	B-cell ALL	1	1.42	1	None	(1) Undetectable
4‡	6	Caucasian	T-cell ALL	2	0.78	1	Grade 2	(1) Undetectable
5‡	4	Caucasian	B-cell ALL	1	0.8	2	None	(1) 0.684 (2) 1.114
6§	6	Caucasian	B-cell ALL	1	0.82	2	None on first dose Grade 3 on second dose	(1) Not drawn (2) Undetectable
7	3	Caucasian	B-cell ALL	3	0.67	4	None	(1) 0.974 (2) 1.193 (3) 1.33 (4) 1.742
8‡	17	Hispanic or Latino	B-cell ALL	1	1.84	1	Grade 1	(1) 0.655
9	2	Caucasian	B-cell ALL	2	0.58	1	None	(1) 0.692
10	2	Caucasian	Pre B-cell ALL	1	0.58	1	None	(1) Not drawn
11	19	Caucasian	Early T-cell Precursor ALL	Unknown	2.46	1	None	(1) 0.908
12‡	15	Caucasian	B-cell lymphoblastic lymphoma	3	1.83	5	None	(1) 0.958 (2) 1.126 (3) 0.642 (4) Not drawn (5) 0.984
13	2	Hispanic or Latino	B-cell ALL	2	0.69	2	None on first dose Grade 2 on second dose	(1) Undetectable (2) Undetectable
14	22	Hispanic or Latino	B-cell ALL	2	1.71	1	None	(1) 0.614
15	15	Caucasian	B-cell ALL	2	1.88	1	Grade 3	(1) Undetectable

*Grade based on CTCAE criteria 5.0.

†Asparaginase activity levels assessed 7 to 14 days after 1-bag PEG infusion. An undetectable result is below the lower threshold of detection for the assay of <0.013 IU/mL.

‡Patients were previously reported in a Brief Report by August et al.⁷§Patient 6 received a dose of 2500 units/m² for the first 1-bag PEG infusion and 1000 units/m² on the second infusion following their predetermined oncology treatment protocol.

||Patient had previously received care at an outside hospital and full records were not available.

ALL indicates acute lymphoblastic leukemia; CTCAE, Common Terminology Criteria for Adverse Events; PEG, Pegaspargase.

patients) of the 28 infusions had signs of hypersensitivity reactions that required interventions such as administration of rescue medication(s) and/or pausing of the infusion. Among the 5 infusion reactions, 1 was grade 1, 2 were grade 2, and 2 were grade 3 reactions based on CTCAE 5.0 criteria. The infusion times for the 4 patients who experienced a hypersensitivity reaction and were able to finish the infusion were 219, 222, 251, and 990 minutes. Three of the 5 hypersensitivity reactions occurred on the first 1-bag PEG desensitization the patient received. None of these 3 patients received a subsequent dose. The remaining 2 patients each reacted to their second 1-bag PEG desensitization infusion and similarly did not receive any further pegaspargase doses. Other than a single patient who had their infusion run over 990 minutes secondary to multiple episodes of hypersensitivity reactions and extended pausing of infusion on multiple occasions, no infusion ran longer than 252 minutes.

Of the 27 completed infusions, 16 infusions demonstrated asparaginase activity >0.1 IU/mL within 14 days of receiving the infusion, 6 were undetectable (<0.013 IU/mL), and 6 infusions did not have an appropriate level drawn postinfusion. In total, 9 of the 15 patients (60%) had adequate asparaginase levels on every postdose lab draw that was drawn within the 7- to 14-day window to satisfy the secondary outcome measure. From the 5 patients who had a documented reaction, 4 of these patients had undetectable asparaginase activity levels 7 to 14 days after infusion. Both of the patients who experienced a hypersensitivity reaction during their second 1-bag PEG desensitization had undetectable (<0.013 IU/mL) after their first dose as well after their second dose. The lone patient who had a documented hypersensitivity reaction and still had an asparaginase activity level of >0.1 IU/mL at day 7 to 14 did not require any rescue medications and the only intervention was a pause in the infusion for 12 minutes (grade 1 reaction).

DISCUSSION

The 1-bag desensitization method to pegaspargase described here simplifies nursing administration and pharmacy preparation compared with other published desensitizations that have utilized 3-bag methods. While data on 1-bag desensitization methods in pediatric patients have been published before, this is the largest reported report of this method the authors are aware of. This 1-bag method demonstrated that over half of patients with previous reactions to a standard infusion of pegaspargase could tolerate the infusion and achieve therapeutic asparaginase levels. The planned infusion time of 195 minutes is in line with other reports of pegaspargase desensitization infusions.^{7,10,11} The actual time of infusion being ~ 206 to 225 minutes can be explained by the time it physically takes for the nurse to make 12 infusion rate adjustments on the infusion pump and that every rate adjustment may not have been completed exactly at the 15-minute mark. It is of interest that 4 of the 5 patients that had a hypersensitivity reaction to the desensitization but were able to complete the infusion also failed to achieve adequate asparaginase levels. This may suggest that these patients have high titers of neutralizing antibodies to pegaspargase that both cause the hypersensitivity reaction and neutralize the medication. The data suggest that a reaction to this desensitization protocol makes it highly likely that the patient will not have adequate asparaginase levels postinfusion and will require treatment with Erwinia asparaginase. However, the opposite is not true, as only 60%

of patients who did tolerate the infusion achieved adequate asparaginase levels. Liu et al⁶ identified previously that polyethylene glycol on the pegaspargase moiety serves as the likely antigen leading to hypersensitivity reactions. Therefore, the possibility exists patients that completed the desensitization with subtherapeutic asparaginase levels have antibodies to asparaginase and not simply a reaction to the polyethylene glycol. Of the 5 patients who had a documented hypersensitivity reaction, 4 of these patients had premedications administered within the predefined 75-minute window. The 1 patient who did not, received 3 of the 4 premedications within 75 minutes of the infusion starting. Given the onset and duration of the oral and intravenous premedications, this supports the notion that premedication timing is unlikely to contribute to the rate of hypersensitivity reactions as previously reported.¹⁴

When devising a desensitization protocol for a chemotherapy agent, an additional consideration is drug stability.¹⁵ The package insert for pegaspargase instructs the volume of drug to be added to 100 mL of 0.9% sodium chloride or 5% dextrose and infused over 1 to 2 hours. The reported stability for diluted pegaspargase is 48 hours at 2 to 8°C.¹⁶ However, there is no information regarding an appropriate concentration of pegaspargase in the diluent. In pediatric patients, a range of body surface areas of 0.5 to 2 m² with a pegaspargase dose of 2500 units/m² would yield an expected range of doses of ~ 1250 to 5000 units. A recommended volume of 100 mL with these doses would mean a final concentration of ~ 12.5 to 50 units/mL. Of the 16 patients who achieved an appropriate asparaginase level in this study, the pegaspargase product had a final concentration of 1.95 to 6.4 units/mL. All the infusions in this study began within 4 hours of compounding the medication. The results are in line with other pegaspargase desensitization protocols with adequate asparaginase activity documented after infusions that had lower concentrations than the package insert would suggest.^{7,8,10,11}

There were several limitations to this study. First, this is a retrospective chart review at a single institution with a small sample size. Second, reporting of pegaspargase reactions is limited to documentation by nurses and providers in the electronic medical record, so there exists the possibility of underreporting the number of reactions that occurred. Finally, the stability of the dilute pegaspargase solution was not evaluated by high performance liquid chromatography or other analytical means to ensure drug potency.

Asparaginase is vitally important to the success of therapy in pediatric acute lymphoblastic leukemia and lymphoblastic lymphoma. When Erwinia asparaginase is unavailable, patients with hypersensitivity reactions to standard pegaspargase infusions have to choose between omitting this important therapy and attempting desensitization. This desensitization protocol differentiates itself in the use of a single bag of pegaspargase for the entire infusion compared with a 3-bag method described in several other studies. This report is the largest single report of efficacy with follow up asparaginase levels that the authors are aware of. While only 60% of the included patients were able to successfully tolerate the infusion and have therapeutic levels, the results are in line with other reports of efficacy in pegaspargase desensitizations. This demonstrates the viability of a 1-bag PEG desensitization when Erwinia asparaginase therapy is unavailable or in short supply. Future directions include direct comparisons between 1-bag and 3-bag methods in a prospective manner to assess if any differences in tolerability or efficacy exist and directly

assessing the stability of dilute pegaspargase concentrations utilized in desensitization protocols.

REFERENCES

1. Pession A, Valsecchi MG, Masera G, et al. Long-term results of a randomized trial on extended use of high dose L-asparaginase for standard risk childhood acute lymphoblastic leukemia. *J Clin Oncol*. 2005;23:7161–7167.
2. Asselin BL. The three asparaginases. Comparative pharmacology and optimal use in childhood leukemia. *Adv Exp Med Biol*. 1999;457:621–629.
3. Tong WH, van der Sluis IM, Alleman CJ, et al. Cost-analysis of treatment of childhood acute lymphoblastic leukemia with asparaginase preparations: the impact of expensive chemotherapy. *Haematologica*. 2013;98:753–759.
4. Hasan H, Shaikh OM, Rassekh SR, et al. Comparison of hypersensitivity rates to intravenous and intramuscular PEG-asparaginase in children with acute lymphoblastic leukemia: a meta-analysis and systematic review. *Pediatr Blood Cancer*. 2017;64:81–88.
5. Burke MJ, Devidas M, Maloney K, et al. Severe pegaspargase 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;59:1624–1633.
6. Liu Y, Smith CA, Panetta JC, et al. Antibodies predict pegaspargase allergic reactions and failure of rechallenge. *J Clin Oncol*. 2019;37:2051–2061.
7. August KJ, Farooki S, Fulbright JM, et al. Desensitization to pegaspargase in children with acute lymphoblastic leukemia and lymphoblastic lymphoma. *Pediatr Blood Cancer*. 2020;67:e28021.
8. Verma A, Chen K, Bender C, et al. 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;36:277–286.
9. Marini BL, Brown J, Benitez L, et al. A single-center multidisciplinary approach to managing the global *Erwinia* asparaginase shortage. *Leuk Lymphoma*. 2019;60:2854–2868.
10. Concha S, Barriga F, Ovalle P, et al. A 12-steps desensitization protocol for pediatric patients with hypersensitivity to pegylated asparaginase. *Ann Allergy Asthma Immunol*. 2020;124:208–210.
11. Swanson HD, Panetta JC, Barker PJ, et al. Predicting success of desensitization after pegaspargase allergy. *Blood*. 2020;135:71–75.
12. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 2017. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. Accessed December 12, 2020.
13. 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;101:279–285.
14. Cooper SL, Young DJ, Bowen CJ, et al. Universal premedication and therapeutic drug monitoring for asparaginase-based therapy prevents infusion-associated acute adverse events and drug substitutions. *Pediatr Blood Cancer*. 2019;66:e27797.
15. Castells M. Rapid desensitization of hypersensitivity reactions to chemotherapy agents. *Curr Drug Saf*. 2006;1:243–251.
16. Oncaspar (pegaspargase) injection label. 2011. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103411s51261bl.pdf. Accessed December 4, 2020.