

Allergic Reactions With Intravenous Compared With Intramuscular Pegaspargase in Children With High-risk Acute Lymphoblastic Leukemia: A Population-based Study From the Maritimes, Canada

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Summary: Intravenous (IV) administration of pegaspargase in children with acute lymphoblastic leukemia (ALL) may be associated with an increased risk of allergic reactions, and thus the need for more costly intramuscular (IM) erwinia asparaginase. In 128 patients allergic reactions were documented in 3% and 14% of those who received IM and IV pegaspargase, respectively ($P = 0.029$). These reactions were primarily contributed to by high risk (HR)-ALL patients ($P < 0.01$). The possible decreased efficacy and quality of life and the substantial costs entailed by switching from IV pegaspargase to IM erwinia should prompt reconsideration of the IV administration route for pegaspargase in HR-ALL patients.

Key Words: pegaspargase, allergic reaction, acute lymphoblastic leukemia, children, intravenous, intramuscular

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L-Asparaginase, most frequently initially administered in its pegylated form (pegaspargase), is a necessary component of the treatment for acute lymphoblastic leukemia (ALL) in children.^{1,2} Several studies describe a higher incidence of hypersensitivity reaction to pegaspargase given intravenous (IV) (19% to 36%) versus intramuscular (IM) (9% to 12%).^{3–6} These studies report patients with relatively small numbers of IV exposures and none describe the economic consequences of reactions.

The impact on care for patients who react to pegaspargase is significant. Patients who react are commonly switched to erwinia asparaginase, an agent with a shorter half-life.^{7,8} Six doses of erwinia are given for every dose of pegaspargase. Erwinia asparaginase is given IM to avoid the increased incidence of anaphylaxis with IV administration.⁸ In addition, it is recommended to monitor serum asparaginase activity levels in all patients receiving any formulation of asparaginase to monitor efficacy.^{9,10} At the study institution pegaspargase was switched from IM to IV

administration in May 2011 in accordance with the Children's Oncology Group (COG).

There is conflicting evidence as to whether patients with high risk (HR)-ALL are more susceptible to an allergic reaction to pegaspargase than standard-risk (SR) patients.¹¹ The present study further explores the incidence and pattern of allergic reactions to IV compared with IM pegaspargase in HR and SR children with ALL. We also describe the estimated costs associated with these reactions, which have not previously been reported.

METHODS

Setting

The IWK Health Centre is a Canadian institution that manages patients from the provinces of Nova Scotia, New Brunswick, and Prince Edward Island. The study period was January 2005 to December 2013. Ethics approval was obtained from the IWK Research Ethics Board.

Hospital Database

Demographic and treatment-related data including experience with pegaspargase for all consecutive children diagnosed with HR or SR ALL, as described by contemporaneous COG protocols in the study period, were retrieved from the patient hospital database.

Inclusion Criteria

All children diagnosed with ALL in the study period who received any asparaginase product by either the IM or IV route.

Asparaginase Dose and Administration

The dose of pegaspargase was 2500 IU/m² IV or IM. Pegaspargase given IV was administered diluted in 100 mL of normal saline, over 2 hours. The dose of erwinia was 20,000 IU/m² × 6 doses IM in place of each dose of pegaspargase. The frequency of administration was based on the COG protocols. All patients were monitored for allergic reactions for 1 hour after the end of the IV infusion and 2 hours after the end of the IM administration of asparaginase. Families were also instructed to report immediately any signs and symptoms of reaction after leaving the hospital. Allergic reactions were managed per standard medical care.

Identification and Grading of Reaction

The grading of the reactions was completed by the attending pediatric oncologist using the Common

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TABLE 1. Incidence of Reactions With IM and IV PEG

Leukemia Risk	Allergic Reactions (n/N [%])			P
	Total	IV PEG Only (51/128)	IM PEG Only (77/128)	
HR (38/128)	9/38 (24)	7/16 (44)	2/22 (9)	0.021
SR (90/128)	0/90 (0)	0/35 (0)	0/55 (0)	—
Total (N = 128)	9/128 (7)	7/51 (14)	2/77 (3)	0.029

HR indicates high-risk acute lymphoblastic leukemia; IM, intramuscular; IV, Intravenous; PEG, pegaspargase; SR, standard-risk acute lymphoblastic leukemia.

Terminology Criteria for adverse events version 3 before 2009 and version 4 after 2009.^{12,13} Medical records of all patients with allergic reaction were reviewed and grading was verified.

Cost Estimates

Any analysis was performed that estimated the costs had all HR patients been treated with IM pegaspargase versus IV from the outset. We used the assumption of a lower incidence of allergic reaction to IM pegaspargase of 10% versus 35% to IV as described in the literature. We used the following assumptions in determining the cost estimates for drug changes related to allergic reaction: Pegaspargase CD\$4460/3750 IU vial and erwinia CD\$1040/10,000 IU vial.

Statistics

Descriptive statistics were used. Variables potentially related to allergic reactions were defined a priori and included lineage of the leukemia, sex and age of the child, treatment protocol, and the dose number to which the patient reacted.

Comparison of incidence of allergic reactions in various patient groups was performed with the Fisher exact test and univariate analysis. SPSS version 22 was used. A *P*-value of <0.05 was considered significant.

RESULTS

A total of 128 children with ALL (SR-ALL = 90, HR-ALL = 38) were identified. For a comparison of the incidence of reactions with IM and IV pegaspargase

see Table 1. No SR patients reacted to asparaginase and 9/38 (24%) of the HR patients reacted. The difference between the reaction to HR versus SR is statistically significant on univariable analysis with odds ratio (95% confidence interval) of 7.8 (1.34-45.1, *P* = 0.022). Of the HR patients who reacted, 7/16 (44%) reacted to IV asparaginase and 2/22 (9%) reacted to IM asparaginase. Patient demographics, treatment protocol, and grade of reaction are described in Table 2.

Most of the reactions to IV pegaspargase occurred within minutes of exposure to the primed solution and resolved after receipt of antihistamines. The 2 grade 4 reactions required epinephrine, antihistamine, and steroid administration; 1 child was observed in the ICU overnight.

The only clinical factor associated with an increased incidence of allergic reactions was the ALL risk group (*P* = 0.02). Neither lineage of the leukemia nor sex was significantly associated with an increased incidence of allergic reactions. Patients who reacted with the third or higher dose had a more severe reaction.

The dose of pegaspargase is 2500 IU/m². On the basis of BSA = 1 m², this equates to CD\$8920 for a SR-ALL patient who receives 2 doses and \$31,220 for a HR-ALL patient who receives 7 doses. In contrast, the cost of erwinia, if added after a reaction to the IV dose 2 or 3 of pegaspargase, would increase from CD\$31,220 to \$102,520 or \$88,260, respectively.

The asparaginase cost per patient in this study for those without an allergic reaction was \$31,220 versus those with allergic reactions, \$95,430 (the average cost per patient based on dose number to which the patient reacted).

TABLE 2. Clinical Characteristics and Allergic Reaction Data to PEG

UPN	Sex	Age*	Lineage†	Risk Group‡	Protocol COG	Reaction Grade CTC 3§	Reaction Grade CTC 4	Dose of PEG Reacted	Interval Between Doses (d)
IM PEG									
1	M	7	T	High	0434	2	2	2/7	61
2	F	10	B	High	0232	3	2	2/7	47
IV PEG									
3	M	12	B	High	0232	4	4	3/7	47.35
4	F	4	B	High	0232	2	2	3/7	50.42
5	F	17	B	High	0232	2	2	1/7	—
6	M	3	B	High	0232	3	2	2/7	45
7	F	10	B	High	0232	2	2	2/7	50
8	M	2	B	High	1131	2	2	3/7	46.27
9	M	15	B	High	0232	4	3	3/7	48.34

*Age in years at time of reaction.

†Classification based on immunophenotype of the leukemia.

‡Leukemia risk group.

§Each reaction was graded using CTC 3 or 4 and compared.

COG indicates Children's Oncology Group; CTC, Common Terminology Criteria; IM, intramuscular; IV, Intravenous; PEG, pegaspargase; UPN, unidentified patient number.

TABLE 3. Results of the Retrospective Chart Review Studies Comparing Allergic Reactions in Children Receiving Either IV or IM Pegaspargase

References	Population	Proportion of Patients with Allergic Reactions (n/N [%])		Findings
		IM	IV	
August et al ³	43 patients with ALL	3/27 (11.1)	2/16 (912.5)	No significant difference in allergic reactions (OR = 2.5; 95% CI, 0.6-11.4)
Petersen et al ⁴	318 patients with ALL	17/159 (10.7)	31/159 (19.5)	Significant increase in allergic reactions for IV vs. IM ($P = 0.028$)
Pidaparti and Bostrom ⁵	197 patients with ALL	17/186 (9)	4/11 (36)	Significant increase in allergic reactions for IV vs. IM ($P = 0.019$) and for HR-ALL vs. SR-ALL (16 vs. 6%, $P = 0.034$)
Abbott et al ⁶	109 patients with ALL	8/69 (12)	14/40 (35)	Significant increase in allergic reactions for IV vs. IM ($P = 0.011$) and for HR-ALL vs. SR-ALL (31 vs. 11%, $P = 0.025$)

ALL indicates acute lymphoblastic leukemia; CI, confidence interval; HR, high-risk acute lymphoblastic leukemia; IM, intramuscular; IV, intravenous; OR, odds ratio; SR, standard-risk acute lymphoblastic leukemia.

We found the estimated drug costs to be \$38,641/patient versus \$56,286/patient for a default IM versus IV route, a difference of approximately 30% (based on the patients reacting to the second dose).

DISCUSSION

The present study demonstrates a significantly increased incidence of allergic reactions in HR-ALL patients receiving IV pegaspargase compared with IM. The patients who reacted to IV pegaspargase received erwinia IM, 6 doses per dose of pegaspargase. This required up to 30 IM doses of erwinia to complete the therapy.

Four studies have been reported in the literature (shown in Table 3) that have shown similar results. There are all retrospective chart reviews and 3 report approximately a 35% incidence of reaction to IV and 10% to IM pegaspargase. The fourth study by August and colleagues showed a similar incidence to our study with 12.5% reaction to IV and 11% to IM pegaspargase. This study had fewer participants as was the case with our study. The lower number of participants is a limitation of this study. Interestingly, 3/5 of the studies, including this study, reported a significantly higher incidence of reactions in the HR-ALL group.

Even though asparaginase is provided free of charge to families in Canada, several factors should be considered when deciding the appropriateness of giving pegaspargase through the IV route. The first is decreased quality of life from subsequent IM injections for those who experience reactions. Second, the higher cost of the use of erwinia asparaginase to the families due to the need for increased visits to hospital and the health care system when allergic reactions occur is significant.¹⁴ Although we recognize that drug costs vary based on manufacturer cost changes and local contracts, we demonstrate that, in our population, the cumulative cost of treatment increased by 30% for drug expenses alone. A third factor to consider is the slightly lower efficacy of erwinia asparaginase compared with pegaspargase, which may possibly alter outcomes.¹⁵

The results of this study add to the growing body of literature suggesting a link between hypersensitivity reactions to IV pegaspargase in children with HR-ALL. We observed 2 patients with grade 4 reactions at their third

exposure to pegaspargase. A larger number of patients are needed to determine whether increased numbers of exposures and a short length of time between exposures worsens reactions.

Anti-asparaginase antibody levels have been correlated with undetectable asparaginase activity, which may be correlated with adverse outcomes in the HR-ALL population.¹¹ We did not monitor activity levels of asparaginase after the reaction, so it is unknown whether the patients in our cohort maintained asparaginase activity. It is unknown whether IV administration of asparaginase may unmask hypersensitivity reactions to asparaginase, which would have been silent if pegaspargase was given IM. The best way to determine this is to monitor asparaginase activity after all doses of asparaginase, regardless of route of administration or degree of severity of reaction.

No reactions were seen in the SR-ALL group. This may be due to the long interval between the 2 doses administered, allowing time for the immune response to attenuate. Perhaps the higher number of doses given to the HR-ALL group led to a higher incidence of reactions and is not disease related. Or perhaps the difference in the steroid given to the HR versus SR patients plays a part in the incidence and grade of reaction. The emerging literature supports that HR patients are at higher risk and that there are substantial drug cost implications and likely increased financial burden to the family. The question that follows is whether the route or schedule needs modification, and whether therapeutic drug monitoring for asparaginase activity is warranted.

CONCLUSIONS

The weight of published evidence and our description of costs of allergic reactions to pegaspargase should prompt reconsideration of the IV route of administration of pegaspargase in the treatment of children with HR ALL. A study designed to prospectively track allergic reactions and their predictive impact on asparaginase activity levels is merited.

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