

Allergic Reactions Associated with Intravenous Versus Intramuscular Pegaspargase: A Retrospective Chart Review

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Abstract

Background Pegaspargase (PEG-ASP) is essential chemotherapy for acute lymphoblastic leukemia (ALL). Since changing to intravenous (IV) administration from intramuscular (IM), an increased number of allergic reactions have been anecdotally noted at our institution. This study compares the rate and severity of allergic reactions in children receiving IM or IV PEG-ASP.

Methods We performed a retrospective chart review of patients treated with IV or IM PEG-ASP at The Hospital for Sick Children, Toronto, Canada, from March 1, 2010 to January 1, 2012. The incidence and severity of allergic reactions attributed to PEG-ASP were documented. Patient age, sex, route of PEG-ASP administration, disease (risk group and lineage) and mean time interval between PEG-

ASP doses were evaluated as possible risk factors for allergic reaction.

Results A total of 109 patients were included. There were 14 (35 %) allergic reactions among 40 patients who received IV, compared with eight (12 %) of the 69 who received IM [odds ratio (OR) 4.11, 95 % confidence interval (CI) 1.54–10.97, $p = 0.005$]. In multivariable logistic regression adjusting for disease risk group, route (IV vs. IM) remained independently significant ($p = 0.011$). Patients with standard-risk ALL had a lower risk of experiencing an allergic reaction associated with PEG-ASP compared with patients in high-risk disease risk groups (collectively referred to as “other”; 11 vs. 31 %, OR 3.36, 95 % CI 1.16–9.72, $p = 0.025$).

Conclusions IV PEG-ASP is associated with a significantly higher rate of allergic reactions than IM. The clinical preference for IV PEG-ASP may warrant re-evaluation.

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Key Points

Route of administration [intravenous (IV) vs. intramuscular (IM)] and disease risk group (high-risk disease risk groups vs. standard-risk disease group) were associated with an increased risk of allergic reactions to pegaspargase (PEG-ASP) in children with acute lymphoblastic leukemia.

Age, sex and lineage of leukemia (T vs. B cell) were not associated with an increased risk of reaction.

The clinical preference for IV PEG-ASP warrants re-evaluation, and strategies for managing asparaginase (ASP) therapy in children with PEG-ASP allergy, including the role of ASP activity monitoring, must be developed.

1 Introduction

Asparaginase (ASP) is a proteolytic enzyme that is a universal component in modern acute lymphoblastic leukemia (ALL) treatment protocols [1–4]. Three types of ASP products are currently administered in North America: *Escherichia coli* ASP [L-asparaginase (L-ASP)], pegylated L-ASP [pegaspargase (PEG-ASP)] and *Erwinia* ASP. As foreign proteins, administration of any of the three ASP products entails a risk of allergic reactions [5]. However, conjugation or pegylation of *E. coli* ASP to monomethoxy polyethylene glycol to form PEG-ASP has been reported to greatly reduce antibody development directed toward ASP, thus decreasing its immunogenicity [3, 6, 7]. Furthermore, PEG-ASP has a long duration of activity and can be given less frequently than L-ASP or *Erwinia* ASP. As a result, PEG-ASP is the preferred ASP product in most North American oncology centers.

Intravenous (IV) administration of *E. coli* ASP was associated with an unacceptable incidence (23 %) of anaphylactic-type allergic reactions [8]. PEG-ASP was therefore initially recommended to be administered by intramuscular (IM) injection. However, recent reports of low rates of clinically apparent allergic reactions following IV administration of PEG-ASP in non-comparative studies has led the pediatric oncology community to adopt IV administration as the preferred route for PEG-ASP [9, 10].

IV PEG-ASP was implemented as the standard of care at The Hospital for Sick Children, in Toronto, Canada, on February 1, 2011, and our institutional standard for the duration of PEG-ASP infusion was set at 90 min. Soon after, clinicians began to remark that allergic reactions, including anaphylaxis, seem to be more frequent and more severe than had been noted when PEG-ASP had been given by IM injection.

The primary objective of this retrospective chart review was to compare the incidence of allergic reactions following IV versus IM PEG-ASP at our institution. The secondary objectives of this study were to (1) describe the nature of allergic reactions associated with PEG-ASP administration; (2) explore potential risk factors for allergic reactions to PEG-ASP; and (3) undertake a review of published, comparative reports of allergic reactions after IM and IV PEG-ASP administration.

2 Methods

We conducted a retrospective chart review of patients who received PEG-ASP from March 1, 2010 to January 1, 2012 at The Hospital for Sick Children. Patients were identified using the pharmacy dispensing database. This study was approved by the Research Ethics Board, The Hospital for Sick Children.

Patient eligibility criteria included any patient who had received either IV or IM PEG-ASP exclusively during the study period. Patients who received both IV and IM PEG-ASP during their treatment course were excluded. Data elements abstracted from the health record included age, weight, height, sex, diagnosis, date of diagnosis, treatment protocol, total number of PEG-ASP doses given until completion of therapy or death, and route of administration (IV or IM). Patients with ALL were classified according to their disease risk group at the time of diagnosis: standard-risk ALL (SR-ALL) or “other” [high-risk (HR), very high-risk, infant or T-cell ALL]. Patients were considered to have experienced an allergic reaction when an acute adverse reaction was documented as such in the health record and attributed to PEG-ASP by the clinicians who documented the reaction. If an allergic reaction occurred, information was obtained regarding the PEG-ASP dose (administration date and time, intended infusion duration, reaction date and time, proportion of PEG-ASP dose administered prior to the reaction, place in protocol, number of previous PEG-ASP doses received) and the allergic reaction (description of reaction, treatments given, i.e., epinephrine, steroids, other). Mean time interval between PEG-ASP doses was calculated by dividing the time period between administration of the first PEG-ASP dose and the last by the number of PEG-ASP doses given during this time period. Allergic reactions were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Supplementary Table 1, online resource 1) [11].

Patient characteristics and outcomes were described using descriptive statistics. Continuous variables were summarized as means and standard deviations, and categorical variables as proportions and confidence intervals (CIs). Categorical variables were compared using the Chi-square or Fisher’s exact tests and continuous variables compared using the Wilcoxon rank sum test. Possible risk factors for allergic reaction to PEG-ASP [route of administration, disease risk group (SR-ALL or “other”), patient age and sex, lineage of leukemia (T or B cell) and mean time interval between PEG-ASP doses] were evaluated. Univariate and multivariable logistic regression were performed to determine if the route of PEG-ASP administration remained independently significant after adjusting for disease risk group. All statistical analyses were conducted using SAS v9.3 (Cary, NC, USA).

We evaluated the effect of time since previous PEG-ASP dose using repeated measures analyses. Since each patient received multiple doses of PEG-ASP, we created one record for each patient at each dose, and created a variable for “days since previous dose” (excluding each patient’s first dose). We fit a regression model including this variable using generalized estimating equations as implemented by SAS Proc GENMOD.

3 Results

During the 22-month study period, 140 patients were identified as having received PEG-ASP. Of these patients, three were excluded since they had received initial chemotherapy treatment at another institution and details of their treatment experience were not available. A further 26 patients were excluded from analysis since they had received both IM and IV PEG-ASP during their treatment course. An additional two patients who had received prior therapy with L-ASP were excluded. Information regarding the remaining 109 patients is presented in Table 1. A total of 22 patients (20 %) experienced an allergic reaction attributed to PEG-ASP. Fourteen of 40 patients reacted to IV PEG-ASP (35 %), while eight of 69 patients reacted to IM PEG-ASP (12 %) [odds ratio (OR) 4.11, 95 % CI 1.54–10.97, $p = 0.005$].

All children who reacted to PEG-ASP had done so by the fourth dose, regardless of the route of administration. Four children reacted to the first dose, 12 children reacted at the time of the second dose, five children reacted with the third dose, and one did so with the fourth dose (Fig. 1). There were no allergic reactions reported to any PEG-ASP dose after the fourth dose. All allergic reactions attributed to PEG-ASP were grade 2 or 3 reactions (Table 2). The difference in reaction severity between groups did not reach statistical significance (Table 2). Time to allergic reaction after IV versus IM administration was not statistically significant (Table 2).

In univariate analysis, IV PEG-ASP was associated with significantly more allergic reactions than IM PEG-ASP (OR 4.11, 95 % CI 1.54–10.97, $p = 0.005$). Patients in the high-risk (“other”) disease risk group had a higher risk of experiencing an allergic reaction associated with PEG-ASP compared with patients in the SR-ALL group (11 vs. 31 %; OR 3.78, 95 % CI 1.35–10.59, $p = 0.012$). In multivariable analysis adjusting for disease risk group (SR-ALL vs. “other”), the effect of route of administration remained independently significant (OR 3.69, 95 % CI 1.34–10.12, $p = 0.011$) (Table 3). Gender, age, and lineage of leukemia (T vs. B cell) were not associated with an increased risk of reaction.

Repeated measures analysis did not show a significant correlation between the mean time interval between PEG-ASP doses and risk of reaction ($p = 0.75$).

4 Discussion

We observed significantly more allergic reactions in patients who received IV PEG-ASP compared to those who received IM PEG-ASP (35 vs. 12 %, OR 3.69, 95 % CI 1.34–10.12, $p = 0.011$). The increased risk of allergic reaction associated with IV PEG-ASP observed in our patients is consistent with other published reports (Table 4) [5, 12–14].

Of the four studies that compared the rates of allergic reaction in children receiving IV versus IM PEG-ASP, all

Table 1 Characteristics of patients who received either IM or IV PEG-ASP and were included in the retrospective review

Characteristic	All patients [$N = 109$]	IM group [$N = 69$]	IV group [$N = 40$]
Continuous variables: mean (range)			
Age at diagnosis (years)	5.9 (0.03–17.4)	5.7 (0.03–17.4)	6.2 (0.6–16.9)
Number of PEG-ASP doses received prior to allergic reaction ^a	3.16 (1–11)	3.17 (1–11)	3.15 (1–7)
Categorical variables: number (%)			
Sex			
Male	60 (55)	39 (57)	21 (53)
Female	49 (45)	30 (43)	19 (47)
Disease type			
SR-ALL	57 (51)	40 (58)	17 (43)
HR-ALL ^b	34 (31)	16 (23)	17 (43)
Infant ALL	4 (4)	3 (4)	0 (0)
T-cell ALL	14 (13)	9 (13)	5 (13)
NHL	2 (2)	1 (1)	1 (3)
Allergic reaction			
Yes	22 (20)	8 (12)	14 (35)
No	87 (80)	61 (88)	26 (65)

ALL acute lymphoblastic leukemia, HR-ALL high-risk acute lymphoblastic leukemia, IM intramuscular, IV intravenous, NHL non-Hodgkin's lymphoma, PEG-ASP pegaspargase, SR-ALL standard-risk acute lymphoblastic leukemia

^a Includes total PEG-ASP doses given to all patients, including patients with no allergic reactions

^b Includes very high-risk ALL

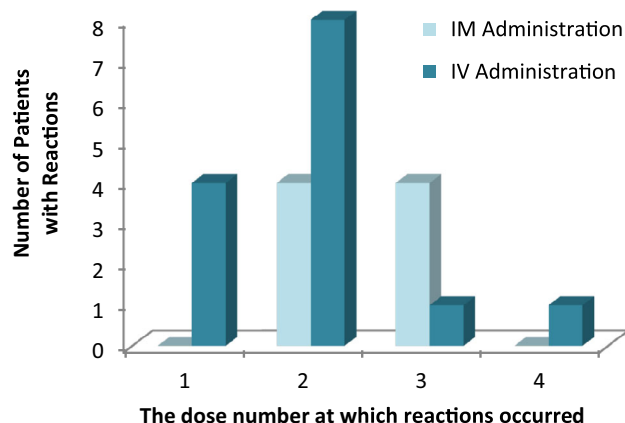


Fig. 1 The dose number of PEG-ASP at which allergic reactions occurred in patients aged <18 years. No reactions were reported after the fourth dose. *IM* intramuscular, *IV* intravenous, *PEG-ASP* pegaspargase

but one observed a statistically higher rate of reaction in children who received IM PEG-ASP. August et al. [13] observed no difference in the rate of allergic reaction based on route of PEG-ASP administration. The reason for the discrepancy between the results of August et al. [13] and other published reports, including our study, is unclear. Factors which have been identified by others which may predispose patients to PEG-ASP allergy, such as disease risk group, were not reported. Sampling bias may play a role since only 16 patients receiving IV PEG-ASP were included. An as yet unappreciated risk factor relating to IV administration, such as infusion duration, administration rate or type of IV pump, may also influence the risk of allergic reaction.

In our study, children enrolled on different protocols received a total of one to 11 PEG-ASP doses. Our data suggest that reactions are most common with the earlier

doses of PEG-ASP since most reactions occurred with the second dose and all reactions had occurred by the fourth dose. This is in contrast to the commonly accepted principle that allergic reactions occur more frequently with repeated, intermittent exposure [15]. August et al. [13] also observed allergic reactions early in the course of PEG-ASP treatment, most commonly with the second PEG-ASP dose.

Contrary to the anecdotal reports that prompted this review, we observed no difference in reaction severity after IV administration compared to IM administration (Table 2). The lack of difference in severity of allergic reactions is consistent with other reports [5, 12, 13]. The difference in time to onset of the allergic reaction was also not statistically significant between the two groups (Table 2). However, patients who received IM PEG-ASP were monitored in clinic for 1 h following dose administration, whereas patients who received IV PEG-ASP were monitored for a total of 2.5 h (during the 1.5-h infusion of the dose and for 1 h afterwards). As a result, more of the reactions associated with IV PEG-ASP in our patients were likely witnessed by health care providers, whereas reactions associated with IM PEG-ASP were more likely to be witnessed by family caregivers. This perhaps led to the impression of health care providers that IV doses were associated with more severe reactions. Petersen et al. [12] reported a higher proportion of allergic reactions which occurred within 30 min of dose administration in children receiving IV compared to IM PEG-ASP (96.3 vs. 18.2 %, $p < 0.001$). The median time to allergic reaction in our patients was 30 and 75 min in the IV and IM PEG-ASP groups, respectively.

Of the possible risk factors for PEG-ASP allergic reaction evaluated other than route of administration, disease risk group was the only factor associated with a significant difference in the incidence of allergic reactions to PEG-

Table 2 Characteristics of allergic reactions experienced by patients who received either IM or IV PEG-ASP

Characteristic	All patients [N = 109]	IM group [N = 69]	IV group [N = 40]	<i>p</i> value
Categorical variables: number (%)				
Grade of reaction				
Grade 1	0	0	0	0.11
Grade 2	13 (59)	3 (37.5)	10 (71)	
Grade 3	9 (41)	5 (62.5)	4 (29)	
Grade 4	0	0	0	
Continuous variables: median (range)				
Time to allergic reaction (min)	61 (38, 5–225)	90 (75, 25–210)	48 (30, 5–225)	0.09
Proportion of ordered PEG-ASP dose received prior to reaction (%)	61 (56, 6–100)	100	38 (34, 6–100)	<0.001
Protocol day of reaction (days)	71 (60, 5–182)	64 (74, 46–95)	69 (53, 5–182)	0.32

IM intramuscular, *IV* intravenous, *PEG-ASP* pegaspargase

Table 3 Univariate and multivariable analysis of predictors of allergic reactions

Characteristic	Incidence of allergic reactions (%)	Univariate OR (95 % CI; <i>p</i> value)	Multivariable OR (95 % CI; <i>p</i> value)
Route of PEG-ASP administration		4.11 (1.54–10.97; <i>p</i> = 0.005)	3.69 (1.34–10.12; <i>p</i> = 0.011)
IM	8/69 (12)		
IV	14/40 (35)		
Disease group		3.78 (1.35–10.59; <i>p</i> = 0.012)	3.36 (1.16–9.72; <i>p</i> = 0.025)
SR-ALL	6/57 (11)		
Other ^a	16/52 (31)		

CI confidence interval, IM intramuscular, IV intravenous, OR odds ratio, PEG-ASP pegaspargase, SR-ALL standard-risk acute lymphoblastic leukemia

^a Other = high-risk and very high-risk acute lymphoblastic leukemia, infant acute lymphoblastic leukemia, T-cell acute lymphoblastic leukemia, and non-Hodgkin's lymphoma

ASP, with patients in the SR-ALL group having a significantly decreased incidence compared with those in the “other” disease risk group. It is doubtful that HR-ALL itself is a risk factor for PEG-ASP allergic reactions. Generally speaking, SR-ALL treatment protocols include fewer PEG-ASP doses than do HR-ALL protocols. In addition, the intervals between PEG-ASP doses are usually longer in SR-ALL protocols than in HR-ALL protocols. However, in our retrospective chart review, repeated measures analysis did not show a significant association between the mean time interval between doses and risk of reaction. It is possible that the difference in risk of allergic reaction is due to the timing of the doses within the treatment protocol and differences in concurrent chemotherapy or corticosteroid therapy.

Pidaparti and Bostrom [5] also observed that patients with HR-ALL had a greater chance of experiencing an allergic reaction to PEG-ASP than did patients with SR-ALL (16 vs. 6 %, *p* = 0.034). This difference was attributed to the greater number of doses administered to patients with HR-ALL compared to patients with SR-ALL [5]. MacDonald et al. [14] also observed that allergic reactions to IV versus IM PEG-ASP occurred significantly more frequently in HR-ALL patients versus SR-ALL (44 vs. 9 %, *p* = 0.021).

It is possible that there is a genetic component to the mechanism of PEG-ASP-induced immune responses [16]. Fernandez et al. [16] recently demonstrated in patients with European ancestry that *HLA-DRB1* alleles are associated with ASP-induced allergic reactions. The *HLA-DRB1*07:01* allele may affect the immune response by influencing the binding affinity of ASP epitopes to *HLA-DRB1* proteins. The *HLA-DRB1* genotype of our patients is unknown, as is the proportion of patients in our study who were of European ancestry.

Product-related factors may also influence the risk of allergic reaction. Pegylation is meant to “mask” ASP from the host's immune system and thereby reduce the immunogenicity and antigenicity of native ASP [17]. However, while

the PEG moiety has been reported to be only weakly immunogenic and non-antigenic, the occurrence of anti-PEG antibodies has also been previously reported [17]. Perhaps exposure to PEG-containing compounds in cosmetics, processed foods and pharmaceuticals may increase the potential for PEG allergy [18]. The likelihood of PEG allergy may be particularly high in children who display a clinical reaction after administration of the first PEG-ASP dose.

Shaking or vigorous agitation of PEG-ASP can lead to high molecular weight aggregates, which may facilitate antigen formation, resulting in reactions (Pamela Famaras, Nucro-Technics, Toronto, Canada, personal communication, November 14, 2013). Though data relating to aggregate formation of PEG-ASP is not available, experience with erythropoietin products indicates that the presence of aggregates may be associated with an increased incidence of reactions [19, 20]. Thus, handling of PEG-ASP during manufacture, shipping and dose preparation may influence the risk of reaction.

The development of anti-ASP antibodies likely results in reduced therapeutic efficacy [21–24]. Patients producing anti-ASP antibodies may or may not manifest a clinical allergic reaction. When no clinical manifestation of an allergic reaction is exhibited, the presence of antibodies and reduced efficacy may not be apparent (silent hypersensitivity). Measuring plasma ASP activity thus becomes an important tool to optimize ASP therapy.

Because of its retrospective nature, this study is limited by the potential of variation and inaccuracy in documentation practices relating to description/severity of allergic reactions and dose administration times. These limitations do not directly relate to our primary objective. It must also be acknowledged that retrospective studies can be biased by cluster effects. That is, it is possible that we and other institutions that decided to study this question were those where an increased rate of reactions in the IV group occurred by chance alone. Therefore, it is important to verify these results in a prospective study.

Table 4 Summary of studies comparing allergic reactions in children receiving either IV or IM PEG-ASP

First author (year of publication)	Study design	Population	Proportion of patients with allergic reactions		Findings
			IM	IV	
August et al. (2013) [13]	Retrospective chart review	Number of patients: 68; 43 patients who received exclusively IV or IM PEG-ASP Mean age in IV group: 6.8 years; range 1.5–14 years Mean age in IM group: 8 years; range 2–19 years Diagnoses: ALL, AML, NHL, LCH	3/27 (11.1 %)	2/16 (12.5 %)	No significant difference between rate of allergic reaction in IV vs. IM PEG-ASP groups (OR 2.5, 95 % CI 0.6–11.4) No difference in severity of reactions between IV and IM groups ($p = 0.25$); all reactions were CTCAE grade 1–3 Patients who reacted to IV PEG-ASP were exposed to more prior doses of asparaginase than those who reacted to IM dosing; reactions occurred after 2nd and 5th doses in IV group, and after 1st, 2nd and 3rd doses in IM group
MacDonald et al. (2014) [14]	Retrospective chart review	Number of patients: 128 Diagnosis: ALL	2/77 (2.6 %)	7/51 (14 %)	Higher rate of allergic reaction in patients receiving IV PEG-ASP ($p = 0.029$) Patients with HR-ALL more likely than SR- ALL patients to experience allergic reactions following PEG-ASP ($p = 0.0001$)
Petersen et al. (2014) [12]	Retrospective chart review	Number of patients: 318 Median age: 5.5 years; 25th–75th percentile 3.2–11.3 years Diagnoses: ALL	17/159 (10.7 %)	31/159 (19.5 %)	Significant increase in incidence of allergic reactions to IV vs. IM PEG-ASP ($p = 0.028$) No difference in severity of reactions between IV and IM groups ($p = 0.862$); all reactions were CTCAE grade 2 (75 %) to 3 (25 %) Time to onset of symptoms of allergic reaction was faster in IV group than in the IM group ($p < 0.001$); less than 30 min for 96 % of patients that received IV PEG- ASP, vs. 18.2 % of patients that received IM PEG-ASP Hospitalization requirement was greater in IM group than in the IV group ($p = 134$); only 12.9 % of patients who received IV PEG-ASP vs. 35.5 % of patients who received IM PEG-ASP required hospitalization Sex, age and lineage of leukemia were not associated with increased risk of infection
Pidaparti and Bostrom (2012) [5]	Retrospective chart review	Number of patients: 197 Mean age: not available Diagnoses: ALL	17/186 (9 %)	4/11 (36 %)	Significant increased incidence of allergic reactions to IV vs. IM PEG-ASP ($p = 0.019$) No difference in reaction severity between IM and IV groups Reactions occurred more often in patients with high-risk malignancy vs. standard risk (16 vs. 6 %; $p = 0.034$)

ALL acute lymphoblastic leukemia, AML acute myelogenous leukemia, CI confidence interval, CTCAE Common Terminology Criteria for Adverse Events, HR-ALL high-risk acute lymphoblastic leukemia, IM intramuscular, IV intravenous, LCH Langerhans cell histiocytosis, NHL non-Hodgkin's lymphoma, OR odds ratio, PEG-ASP pegaspargase, SR-ALL standard-risk acute lymphoblastic leukemia

In conclusion, IV PEG-ASP is associated with a significantly higher rate of allergic reactions than IM administration. Patients with SR-ALL have a lower risk of

allergic reactions. Given our results, re-evaluation of IV PEG-ASP as the preferred route of PEG-ASP administration is needed. Regardless of the route of PEG-ASP

administration, emerging evidence regarding the value of ASP activity monitoring and ASP dose individualization should be evaluated for incorporation into strategies for managing ASP therapy in patients with PEG-ASP allergy.

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