

ORIGINAL ARTICLE

Comparison of Allergic Reactions to Intravenous and Intramuscular Pegaspargase in Children with Acute Lymphoblastic Leukemia

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Pegaspargase (PEG) is a standard component of therapy for pediatric acute lymphoblastic leukemia (ALL). Because PEG preparations are bacterially derived, they are highly immunogenic. PEG has traditionally been delivered intramuscularly (IM), but over the last several years, more PEG has been given intravenously (IV) in order to provide a less painful and more convenient means of delivery. However, there are limited data comparing allergic reactions between IV and IM PEG recipients, especially in a large cohort of patients. We reviewed the charts of pediatric ALL patients diagnosed from 2006 to 2011 who received PEG at our institution and compared the incidence, time to onset of symptoms, reaction grade, and hospitalization rate for patients who had allergic reactions to PEG. Of 318 evaluable patients, 159 received IV and 159 received IM PEG. Thirty-one (19.5%) IV patients had an allergic reaction, compared to 17 (10.7%) IM patients ($P = .028$). Time to onset of symptoms was ≤ 30 minutes for 26 of 27 evaluable IV patients (96.3%) versus only two of 11 evaluable IM patients (18.2%; $P < .001$). Four of 31 IV patients (12.9%) and six of 17 IM patients (35.5%) required hospitalization ($P = .134$). There is increased incidence of allergy in patients who received IV PEG compared to IM. Grade of reaction was similar between IV and IM, but allergic reactions to IV PEG had a more rapid onset. While the risk of allergy may be increased, IV delivery appears to have an acceptable safety profile for administration in ALL patients.

Keywords ALL, allergy, intramuscular, intravenous, pegaspargase

INTRODUCTION

Asparaginase, a bacterial enzyme that depletes serum asparagine levels, is an important component of therapy for pediatric acute lymphoblastic leukemia (ALL) patients [1–3]. Because ALL blast cells are unable to produce asparagine and are dependent on plasma levels of this amino acid for protein synthesis, depletion of serum asparagine

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levels by pegaspargase (PEG) results in apoptotic cell death of blasts due to inhibition of RNA, DNA, and protein synthesis [4, 5].

Because asparaginase preparations are bacterially derived, they are highly immunogenic [6, 7]. In order to help reduce the immunogenic potential, polyethylene glycosylated (PEG)-asparaginase formulations were created by covalently attaching polyethylene glycol to the native *E. Coli* asparaginase enzyme [8]. This resulted in reduced rates of antibody formation, lower incidence of allergy, longer serum half-life, and faster asparagine depletion, making PEG the preferred form of asparaginase in most pediatric ALL protocols [8–13].

PEG has traditionally been delivered intramuscularly (IM) at least in part to help reduce the risk and severity of allergic reactions [14]. Over the last several years, more PEG has been given intravenously (IV) in order to provide a less painful and more convenient means of delivering the drug. It depletes asparagine levels as effectively as IM PEG-asparaginase [9, 10], and small series have demonstrated similar safety profiles after one dose of IV PEG [10, 15].

There are limited data comparing allergy between IV and IM PEG recipients over multiple doses, especially in a large cohort of patients. One report described an increased rate of allergy in pediatric IV PEG recipients compared to IM (36% vs. 19.5%; $P = .019$) with no difference in severity of reaction between IV and IM recipients [16]. However, the sample size was small, as only 11 total IV patients (four allergic) were included in their study. In contrast, a previous report from our institution reported no difference in incidence of allergy between IV and IM PEG (12.5 vs. 11.1%; “ $p =$ not significant”) [17], but again the sample size was small, as only 16 IV patients (two allergic) were evaluated. The current report describes expanded results for a much larger cohort of patients over a longer duration. We compared the incidence, time to onset of symptoms, grade of reaction, and rate of hospitalization for pediatric ALL patients treated at our institution who had allergic reactions to IV and IM PEG.

MATERIALS AND METHODS

We retrospectively reviewed the charts of pediatric ALL patients diagnosed from January 1, 2006 to December 31, 2011 who received IV and IM PEG at the Aflac Cancer and Blood Disorders Center of Children’s Healthcare of Atlanta. We assigned them to either the IV or IM PEG group based on method of PEG they received. For simplicity, we excluded patients who received at least one dose of both IV and IM PEG. Institutional review board approval was obtained.

Allergy data was obtained by retrospective chart review. Allergic reactions were defined and retrospectively graded by study personnel according to the National Institute of Health’s “common toxicity criteria for adverse events” (CTCAE) (version 4.03, published June 14, 2010) based on clinical documentation contained in patients’ charts.

All statistical analyses were performed using SAS 9.2 (Cary, NC), and statistical significance was assessed at the .05 significance level unless otherwise noted. Prior to the analysis, the normality of age was assessed using the Anderson-Darling test for normality and by visual inspection of the histogram. Failing to meet this assumption, the results for age are presented with the median, 25th and 75th percentiles. Discrete variables are represented by frequency counts and percentages.

Descriptive statistics were calculated for all demographic variables and statistical comparisons were made between IV and IM PEG administration. Additionally, differences in demographic variables were investigated between allergic and non-allergic patients. The Wilcoxon rank-sum test was utilized for the continuous age variable and the Chi-square test for independence was used for discrete variables. An exact form of

the Pearson's Chi-square test was implemented when frequency counts were low (less than five).

RESULTS

Patient Characteristics

Of 318 evaluable patients, 159 received IV and 159 received IM PEG. No significant differences were found in age (5.0 vs. 6.3; $P = .096$), gender ($P = .368$), or lineage ($P = .185$) between the IV and IM groups (Table 1).

Allergy

There were a total of 48 patients with allergy to PEG. Thirty-one (19.5%) of 159 IV patients had an allergic reaction, compared to 17 (10.7%) of 159 IM patients ($P = .028$). Clinical characteristics for each of the allergic patients are displayed in Table 2.

There were no significant differences in age (7.4 vs. 5.2; $P = .121$) or lineage ($P = .086$) between allergic and non-allergic patients, but males had a significantly higher incidence of allergy compared to females (72.9% vs. 51.5%; $P = .006$) (Table 3).

Severity of Reaction

All 48 allergic patients' reactions were either grade two or three according to CTCAE criteria (Table 2). There were 36 (75%) total grade two reactions and 12 (25%) grade three reactions. Twenty-three (74.2%) IV patients had a grade two reaction and eight (25.8%) had a grade three reaction, whereas 13 (76.5%) IM patients had a grade two reaction and four (23.5%) had a grade three reaction. There was no statistical difference in grade of reaction between IV and IM patients ($P = .862$) (Table 4).

Onset of Symptoms

Time to onset of symptoms was ≤ 30 minutes for 26 of 27 evaluable IV patients (96.3%) versus only two of 11 evaluable IM patients (18.2%; $P < .001$) (Table 4). This data were not available for four IV and six IM patients. Twenty-three of 27 IV patients (85.2%) had signs of reaction in 10 minutes or less, compared to zero (0%) of 11 IM patients ($P < .001$).

Hospitalization

While not statistically significant, IM patients were admitted to the hospital almost three times as frequently as IV patients (35.3% vs. 12.9%; $P = .134$) (Table 4).

DISCUSSION

While there are data supporting the safety of delivering one dose of PEG via the intravenous route [10, 15], data comparing allergic manifestations between IV and IM

TABLE 1 Demographic Information for IM and IV Patients

Characteristic	Level	Total $N = 318$	IM PEG $N = 159$	IV PEG $N = 159$	P -value
Age median (25th–75th)	–	5.5 (3.2–11.3)	5.0 (3.1–10.2)	6.3 (3.5–13.0)	.096
Gender N (%)	Female	144 (45.3%)	68 (42.8%)	76 (47.8%)	.368
	Male	174 (54.7%)	91 (57.2%)	83 (52.2%)	
Lineage N (%)	B	280 (88.1%)	138 (86.8%)	142 (89.3%)	.185
	T	33 (10.4%)	20 (12.6%)	13 (8.2%)	
	M	5 (1.5%)	1 (0.6%)	4 (2.5%)	
Allergic reactions N (%)	Yes	48 (15.1%)	17 (10.7%)	31 (19.5%)	.028*

TABLE 2 Clinical Characteristics of Allergic Patients

Patient number	Route	Gender	Age at diagnosis (yrs)	Lineage	Reaction grade	Hospital admission	Onset of symptoms (min)
1	IM	F	12	B	3	Yes	360
2	IM	M	4.6	B	2	No	NA
3	IM	M	16	B	2	No	30
4	IM	F	14.8	B	2	No	Several hours
5	IM	F	1.1	B	2	No	50
6	IM	M	5.8	B	2	No	180
7	IM	M	7.3	T	2	No	NA
8	IM	M	16.5	T	2	No	Several hours
9	IM	M	8.9	B	2	No	NA
10	IM	M	1.6	B	2	No	NA
11	IM	M	9.8	T	2	No	Next day
12	IM	M	3.4	B	2	Yes	NA
13	IM	M	7.8	B	3	Yes	165
14	IM	M	2.8	B	2	Yes	NA
15	IM	M	8.7	T	3	Yes	60
16	IM	M	15.7	T	3	Yes	NA
17	IM	M	3.2	B	2	No	30
18	IV	F	2.5	B	2	No	5
19	IV	M	11	B	2	No	5
20	IV	F	6.4	B	3	Yes	NA
21	IV	M	4.1	B	2	No	10
22	IV	M	9.8	M	2	Yes	2
23	IV	M	16.3	T	3	Yes	2
24	IV	M	4.3	B	2	No	30
25	IV	M	17.7	B	2	No	4
26	IV	M	18.1	B	2	No	5
27	IV	F	16.3	B	2	No	5
28	IV	F	1.7	B	2	No	8
29	IV	M	14.9	B	2	No	<10
30	IV	F	15.6	B	3	No	<10
31	IV	M	1.1	B	2	No	NA
32	IV	M	8.4	B	2	No	15
33	IV	F	6.7	B	2	No	5
34	IV	F	1.8	B	3	No	10
35	IV	M	2.4	B	2	No	10
36	IV	M	16.4	B	2	No	<1
37	IV	M	9.5	B	2	No	2
38	IV	F	7.4	B	2	No	2
39	IV	M	6	B	2	No	2
40	IV	M	3.2	B	3	No	2
41	IV	M	3.6	B	3	No	5
42	IV	F	4.1	B	3	No	12
43	IV	M	6.3	B	3	Yes	5
44	IV	M	14.6	B	2	No	<1
45	IV	M	3.9	T	2	No	NA
46	IV	M	4.2	T	2	No	360
47	IV	F	16.1	T	2	No	NA
48	IV	M	8.6	B	2	No	5

Route = route of PEG administration; IM = intramuscular; IV = intravenous; M = male; F = female; B = B cell lymphoblastic; T = T cell lymphoblastic; M = mixed lineage; Reaction grade = grade according to CTCAE version 4.03; NA = not available.

TABLE 3 Demographic Information of Allergic and Non-Allergic Patients

Characteristic	Level	Allergic <i>N</i> = 48	Non-allergic <i>N</i> = 270	<i>P</i> -value
Age median (25th–75th)	–	7.4 (3.8–14.7)	5.2 (3.1–10.4)	.121
Gender <i>N</i> (%)	Female	13 (27.1%)	131 (48.5%)	.006*
	Male	35 (72.9%)	139 (51.5%)	
Lineage <i>N</i> (%)	B	38 (79.2%)	242 (89.6%)	.086
	T	9 (18.7%)	24 (8.9%)	
	M	1 (2.1%)	4 (1.5%)	

PEG, especially in a large cohort of patients over multiple doses, is limited. Our study confirms in a large population of patients that the rate of allergy is significantly higher in IV recipients compared to IM (19.5% vs. 10.7%; $P = .028$). This is consistent with a previous report of increased incidence of allergy in IV compared to IM PEG patients, although their reported incidence was almost twice as high as ours (36% vs. 19.5%; $P = .019$) [16]. This discrepancy may be due to differences in sample size: our study evaluated 159 IV patients (31 allergic) compared to 11 IV patients in their series (four allergic). The incidence reported in our study likely represents a more accurate estimate of the true incidence of allergy in this population. A previous report from our institution found no difference in rate of allergy between IV and IM PEG recipients (12.5% vs. 11.1%; “ $P =$ not significant”) [17]; however, this study was also performed on a smaller subset of patients (16 total IV patients, only two allergic) over a shorter time period, and some of these patients were being treated for diagnoses other than ALL.

The reason for the increased incidence of allergy in IV patients is unclear, especially since there is no pharmacological difference between IV and IM PEG. It is possible that differences in the processing and handling of the IV drug, such as agitation of vials, flow through IV tubing, or dilution with normal saline, make the IV-delivered drug more immunogenic. Differences in immune processing of IV compared to IM PEG may also contribute to differences in immunogenicity. Further studies are needed to better understand the reasons for this difference in incidence of allergy.

While the rate of allergy is higher for patients who received IV PEG, our grading data suggest that the severity of reactions is no different, which is consistent with previous reports [16]. Additionally, although not statistically significant, our IM patients required hospitalization almost three times more often than IV patients did (35.3% vs. 12.9%, $P = .134$). This may suggest that faster detection of allergic reactions during the IV infusion may have enabled providers to limit the amount of drug to which the patient was exposed, thus helping to limit the extent, severity, and duration of patients’ reactions. Additionally, reactions that occur during the infusion can be managed more expediently than those occurring at home. Allergic reactions to IV PEG almost uniformly had a rapid onset. Among our evaluable IV patients, the majority occurred within the first 10 minutes of the infusion (85.2%) compared to zero

TABLE 4 Differences in Rates of Hospitalization, time to Onset of Symptoms, and Reaction Grade Between IM and IV Patients

Characteristic	Level	Total <i>N</i> = 48	IM PEG <i>N</i> = 17	IV PEG <i>N</i> = 31	<i>P</i> -value
Hospital admission <i>N</i> (%)	Yes	10 (20.8%)	6 (35.3%)	4 (12.9%)	.134
Onset of symptoms $\leq$ 30 minutes ¹ <i>N</i> (%)	Yes	28 (73.7%)	2 (18.2%)	26 (96.3%)	<.001*
Reaction grade	2	36 (75.0%)	13 (76.5%)	23 (74.2%)	.862
	3	12 (25.0%)	4 (23.5%)	8 (25.8%)	

¹Data not available for 10 patients (6 IM and 4 IV).

(0%) evaluable IM patients ($P < .001$). All but one evaluable IV patients reacted in 30 minutes or less (96.3%) compared to only two of 11 (18.2%) evaluable IM patients ($P < .001$). As such, prolonged observation for reactions after completion of IV infusions may be unwarranted.

Interestingly, we found a difference in incidence of allergy between male and female PEG recipients, with males having a higher overall incidence of PEG allergy (72.9% vs. 51.5%; $P = .006$). The reason for this is unclear, and of uncertain significance. Prior studies that evaluated incidence of allergy to PEG have not found a difference in incidence between males and females, but numbers were smaller than our study [13, 16, 17].

CONCLUSIONS

While the risk of allergy is increased for IV patients, IV delivery appears to have an acceptable safety profile for administration in ALL patients receiving PEG. Further investigation into reasons why IV delivery is associated with increased incidence of allergy is warranted, as it may shed light on general principles of immunogenicity and impact future PEG drug design and handling procedures, ultimately enabling more ALL patients to receive PEG without allergic manifestations.

Declaration of Interest

D.C. has served as a speaker for Sigma Tau Pharmaceuticals. The remaining authors declare no conflict of interest.

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