

Comparison of Allergic Reactions to Pegasparaginase Given Intravenously Versus Intramuscularly

Mahati Pidaparti and Bruce Bostrom, MD*

Background. Pegasparaginase (PEG) is important for treatment of Acute Lymphoblastic Leukemia (ALL). Despite conjugation to polyethylene glycol to reduce immunogenicity, allergic reactions still occur and may be severe. Traditionally, PEG is given via intramuscular (IM) injection but recent protocols have shown it can be safely given intravenously (IV), which may be preferred by patients. There is a potential concern that the IV route may result in more severe allergic reactions due to immediate exposure to reactive antibodies in the blood, which is delayed after IM administration. The purpose of our study is to compare the severity and incidence of allergic reactions with IV versus IM PEG. We are unaware of any prior studies examining this. **Procedure.** We reviewed all patients with ALL diagnosed from 2005 to 2010 inclusive who received PEG and

had an allergic reaction. Reactions were graded using both common toxicity criteria (CTC) 3.0 and 4.0. **Results.** Allergic reactions were seen in 17 of 186 (9%) newly diagnosed patients receiving IM PEG and 4 of 11 (36%) receiving IV PEG; $P = 0.019$. The severity of reaction was not increased with IV versus IM. Allergic reactions occurred more frequently in high-risk patients (14 of 85; 16%) versus standard risk (7 of 112; 6%), $P = 0.034$. **Conclusions.** There appears to be an increased incidence of allergic reactions in patients who receive IV PEG compared with IM although the severity is similar. In addition high-risk patients appear to have more allergic reactions than standard risk. *Pediatr Blood Cancer* © 2011 Wiley Periodicals, Inc.

Key words: allergic reactions; asparaginase; intramuscular; intravenous; pegasparaginase

INTRODUCTION

Pegasparaginase (pegaspargase; PEG) is an important drug used in the treatment of acute lymphoblastic leukemia (ALL) [1–3]. However, as with all asparaginase preparations due to foreign protein immunogenicity, there is a risk of hypersensitive allergic reactions that may limit its efficacy.

As reviewed by Narta et al. [4], the most common clinical appearance of hypersensitivity is urticaria; however, the variety of allergic reactions ranges from localized erythema to systemic anaphylaxis. As described by Narta et al. [4] hypersensitivity reactions include induration, edema, swelling, chill, fever, tenderness, and skin rashes. Urticaria at times can be treated or prevented with antihistamines; however, other more severe reactions often require discontinuation of the specific form of the drug with substitution of an analog such as Erwinase. Allergic reactions have 13–30% frequency of occurrence for native *E. coli* L-asparaginase (Native). Risk of hypersensitivity to Native includes doses above 6,000 IU/m²/day, intravenous (IV) route of administration rather than intramuscular (IM), repeated courses of treatment and single-agent use. Rate of allergic reactions to PEG is 10% for non-hypersensitive patients and 32% of the patients hypersensitive to Native.

Raetz and Salzer [5] in a recent review have summarized the incidence of clinical hypersensitivity to all three forms of asparaginase when given IM. The incidence of reactions ranged from 1% to 33%. The study with the lowest incidence was CCG 1962 in which patients were randomized to receive either 3 doses of IM PEG versus 21 doses of IM Native. Reactions were seen in none of 59 patients randomized to Native and only 1 of 59 randomized to PEG [6]. Silverman et al. [7] in the DFCI 91-01 protocol reported a 15% incidence of allergic reactions in patients who were randomized to receive Native IM weekly versus PEG IM every 2 weeks for 30 weeks. PEG was associated with a lower incidence of mild allergic reactions although there was no difference between PEG and Native in dose limiting severe allergic reactions.

Patients who receive multiple or repeated doses of Native may have an increased risk of allergic reactions over time. Woo et al. [8], reported 22 patients receiving Native during

induction (9 doses), re-induction (9 doses), and early maintenance (7 doses) developed allergic reactions after a median of 11 doses (range: 4–20). Vrooman et al. [9] found 45 of 215 (21%) patients receiving post-induction Native developed allergic reaction after a median of 5 weekly doses (range: 1–24).

Traditionally, PEG and Native have been given via IM administration. This preference for IM use dates to an early CCG study that compared Native by the IV versus IM routes and found a significant increase in anaphylaxis for IV versus IM although there was no difference in incidence of overall allergic reactions [10]. Indeed, 18 of 80 patients receiving IV (23%) had anaphylaxis versus 0 of 73 following IM. This finding stands in contrast to that seen with antibody induction from foreign proteins where the immunogenicity is felt to be greatest with subcutaneous administration, less with IM and least with IV [11]. Recent studies have shown that PEG can be given IV without significant toxicity [12,13]. Douer et al. [12] treated 25 newly diagnosed adults with induction chemotherapy including a single dose of IV PEG and observed no allergic reactions. Silverman et al. [13] treated 197 newly diagnosed children with a single dose of IV PEG during induction saw allergic reactions in 3 with no anaphylaxis.

METHODS

Patients with ALL who received PEG from 2005 to 2010 inclusive were evaluated for allergic reactions using the electronic medical record (EMR). Following Institutional Review Board approval, we obtained a list of all doses of PEG given to reacting

Pediatric Hematology and Oncology, Children's Hospitals and Clinics of Minnesota, Minneapolis, Minnesota

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*Correspondence to: Bruce Bostrom, MD, Pediatric Hematology and Oncology, Children's Hospitals and Clinics of Minnesota, 2530 Chicago Ave S, CSC 175, Minneapolis, MN 55404.
E-mail: bruce.bostrom@childrensmn.org

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patients from the pharmacy database and a list of patients who developed allergic reactions from the data warehouse. We also obtained additional demographic information relevant to the analysis from the hemonc database or EMR.

Two patients who had an allergic reaction during treatment with IM PEG for relapse were excluded from further analysis; 1 infant and 1 with standard risk ALL. Two patients included in our study enrolled on COG AALL 07P4 received EZN-2285 (UPN 18, 19). UPN 19 received EZN-2285 exclusively while UPN 18 only received EZN-2285 on the first dose with IV PEG thereafter. They were included as part of the IV PEG group.

The EMR was reviewed in all patients who developed an allergic reaction to PEG to determine the severity of the reaction using the common toxicity criteria (CTC) v. 3.0 and 4.0 (Table I). This allows semi-quantification of the severity from 1 to 4, based on accepted standards for allergic reactions. In one case (UPN 9), reaction grade could not be assigned due to lack of documentation. In a second case (UPN 20), reaction grade could not be assigned for CTC 3.0 because the reaction symptoms of nasal congestion and “abnormal throat sensation” are not included in CTC 3.0. In a few cases, the reaction severity could not be unambiguously documented from the information contained in the EMR. In those cases, the assigned reaction grade was averaged between the higher and lower grade for analysis. This was done for CTC 3.0 in 4 patients (UPN 5, 6, 7, 19) and for CTC 4.0 in 1 patient (UPN 1). Most of the ambiguity was differentiating between grades 3 and 4 reactions for CTC 3.0 in 3 patients (UPN 5, 6, 7; Table II).

The allergic reaction grade and other demographic data as listed in Table I were entered in SPSS v. 15.0. Comparison of the grade between CTC 3.0 and 4.0 were done using paired *t*-test for all patients. Comparison of the grade for IM versus IV by CTC 3.0, CTC 4.0, number of PEG doses given, and time from diagnosis to allergy occurrence in months were done using independent samples *t*-test with Levene's test to assess equality of variances.

To determine the incidence of allergic reactions, we obtained the total number of patients with ALL treated from 2005 to 2010 inclusive. Four patients with infant ALL were excluded. We also determined this information by route of administration (IM vs. IV), risk group (standard vs. high), and cell type (T vs. B). Comparisons of incidence of allergic reactions were analyzed using a 2 × 2 contingency table with two-tailed *P*-values from Fisher's exact test.

RESULTS

Comparison of CTC 3.0 Versus 4.0 for Grading Allergic Reactions to PEG

A total of 21 patients were identified as having an allergic reaction to PEG, 17 who received IM and 4 IV (Table II). Reactions could be unambiguously graded using CTC 3.0 in 15 of 19 (79%) cases and using CTC 4.0 in 19 of 20 (95%) cases. There was no difference by paired *t*-test comparing the grading overall using CTC 3.0 or CTC 4.0.

Comparison of the Severity and Incidence of Allergic Reactions With IM and IV PEG

The mean ± standard deviation and median of allergic reaction grade for CTC 3.0 and CTC 4.0, number of doses of PEG, and months from diagnosis to allergic reaction are listed in Table II. The severity using either grading system ranged from 1 to 4 with IM PEG and 1 to 2.5 with IV PEG. Using CTC 3.0, equal variances could be assumed and the *P*-value was not significant. Using CTC 4.0, equal variances could not be assumed because there was no variance in the IV group. The *P*-value was significant at 0.007 with mean value for IV PEG lower than IM.

Comparing the number of PEG doses given and time from diagnosis to allergy by IM versus IV were not significant using independent sample *t*-test with equal variances. A total of 197 non-infant patients were diagnosed with ALL during the time of this study and treated exclusively with PEG or EZN-2285. One hundred eighty-six received IM and 11 received IV. Of the 11, 3 received PEG exclusively, 1 received PEG for the majority of doses (UPN 18), and 7 received EZN exclusively. Four of 11 patients who received IV PEG developed allergic reactions (36%) versus 17 of 186 who received IM (9%). These are significantly different at *P* = 0.019. We looked to see if this difference could be explained by more high-risk patients receiving IV PEG versus IM, which was not the case. A total of 4 of 112 standard risk patients received IV PEG versus 7 of 85 high-risk patients. The *P*-value was not significant at 0.21.

Clinical Factors Associated With Increased Incidence of Allergic Reactions

The only clinical factor associated with an increased incidence of allergic reactions was NCI risk group. Allergic reactions to

TABLE I. Common Toxicity Criteria for Allergic Reactions

Grade	Description for CTC v. 3.0	Description for CTC v. 4.0
1	Transient flushing or rash; drug fever <38°C (<100.4°F)	Transient flushing or rash, drug fever <38°C (<100.4°F); intervention not indicated
2	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤24 hours
3	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)
4	Anaphylaxis	Life-threatening consequences; urgent intervention indicated
5	Death	Death

TABLE II. Clinical Characteristics and Allergic Reaction Data

UPN	Gender	Age of diagnosis	Lineage	NCI risk group	Treatment protocol	Reaction CTC 3.0	Reaction CTC 4.0	Total PEG doses	Diagnosis to allergy
Intramuscular PEG									
1	Female	4.2	B	High	AALL0232	1	1.5	7	3.0
2	Male	4.0	B	Standard	AALL0331	3	3	4	2.6
3	Male	13.1	B	High	AALL0232	2	3	3	2.7
4	Male	5.8	B	Standard	AALL0331	3	3	3	2.6
5	Male	4.2	B	High	AALL0232	3.5	3	2	1.7
6	Female	14.4	B	High	AALL0232	3.5	3	3	3.0
7	Female	17.1	B	High	AALL0232	3.5	3	3	2.9
8	Female	18.2	B	High	AALL0232	4	4	3	2.5
9	Male	15.6	T	High	AALL0434	NG	NG	2	2.9
10	Male	1.4	B	Standard	AALL0331	2	2	2	1.6
11	Male	2.7	B	Standard	AALL0331	1	1	2	4.4
12	Female	1.1	B	High	AALL0232	2	2	4	3.1
13	Female	2.6	B	Standard	AALL0331	3	3	3	2.9
14	Female	10.6	B	High	AALL0232	2	2	2	6.9
15	Male	2.1	B	Standard	AALL0331	2	2	6	4.4
16	Male	5.0	B	High	AALL0232	3	3	3	3.4
17	Female	9.0	B	Standard	AALL0331	3	3	6	4.7
Mean $\pm$ SD						2.6 $\pm$ 0.9	2.6 $\pm$ 0.8	3.4 $\pm$ 1.5	3.2 $\pm$ 1.3
Median						3.0	3.0	3.0	2.9
Intravenous PEG									
18	Male	13.9	B	High	AALL07P4	1	2	3	2.1
19	Male	12.7	B	High	AALL07P4	2.5	2	2	2.0
20	Female	11.3	B	High	AALL0232	NG	2	4	3.8
21	Female	13.7	B	High	AALL07P4	2	2	3	2.8
Mean $\pm$ SD						1.8 $\pm$ 0.8	2.0 $\pm$ 0	3.0 $\pm$ 0.8	2.7 $\pm$ 0.9
Median						2.0	2.0	3.0	2.5

Reaction = grade of allergic reaction with CTC 3.0 or CTC 4.0; Total PEG doses = total number of doses given up to and including the dose where reaction was observed; Diagnosis to allergy = time from ALL diagnosis to allergic reaction in months; SD = standard deviation; NG = not gradeable. UPN 1–17 received intramuscular PEG and UPN 18–21 received intravenous.

either IM or IV PEG were seen in 7 of 112 standard risk patients (6%) versus 14 of 85 high-risk patients (16%). These are significantly different at $P = 0.034$. Neither lineage of the leukemia nor gender was significantly associated with an increased incidence of allergic reactions.

DISCUSSION

We found no significant difference in the severity of allergic reactions to IV versus IM PEG in our study using CTC 3.0. However, there was a significant difference using CTC 4.0 possibly due to the lack of variance in the IV group. If the variances could be assumed to be equal, the difference would not be significant. Our conclusion is that there is no significant difference between the reaction severities with IM versus IV PEG.

However, we did see a significant increased incidence of allergic reactions to IV versus IM PEG. This difference could be related to small numbers of patients who received IV PEG (PEG or EZN-2285). Also, the retrospective nature of this study may have influenced the results, as IV PEG was used only in a more recent group of patients. Because all the patients who received EZN-2285 were by design in the IV group, this could have influenced the outcome if there were differences in the reaction incidence with PEG and EZN-2285. However, reactions

were seen in 2 of 7 patients who received EZN-2285 exclusively and 2 of 4 who received all or the majority of doses as IV PEG. Also there are no reported differences in the incidence of allergic reactions to IV PEG and IV EZN-2285 in the COG AALL07P4 study.

We found that NCI high-risk patients had a greater chance of reacting to PEG irrespective of route with 16% of high risk and 6% of standard risk patients developing an allergic reaction. This difference was not explained by a disproportionate number of high-risk patients receiving IV. This may be due to a greater number of doses received by the high-risk compared to standard risk patients.

We also found that CTC 4.0 resulted in fewer ambiguities in grading the severity of the allergic reactions than CTC 3.0 and thus is the preferred grading system.

In conclusion, we found no significant difference in the severity of allergic reactions to IV versus IM PEG. Our findings of an increased incidence of reactions with IV PEG should be confirmed by analysis of data from large cooperative group trials.

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