

The Incidence of Hypersensitivity Reactions to Pegylated Asparaginase in Children With Acute Lymphoblastic Leukemia: A City-Wide Experience

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Summary: Asparaginase (ASNase) is an imperative component of pediatric acute lymphoblastic leukemia (ALL) therapy. Pegylating the ASNase extends its biological half-life in vivo and has become the only ASNase available in the United States for frontline therapy of ALL and lymphoblastic lymphoma. It is either infused intravenously (IV) or injected intramuscularly (IM), administrations of which are associated with hypersensitivity reaction ranging from localized skin reaction to severe anaphylaxis. A retrospective review of 96 medical records of pediatric ALL patients was performed. We compared the incidence of hypersensitivity reaction associated with IV versus IM administration of pegylated ASNase. Ninety-one patients were included in the final analysis; 31 having received pegylated ASNase IV and 60 receiving it IM. The incidence of any grade ≥ 2 hypersensitivity reaction in patients who received IV ASNase was 32.2% compared with 13.3% in the IM group ($P = 0.032$). There was no difference in higher grade hypersensitivity reactions (19.4% vs. 11.7%). Most reactions tended to occur during periods of leukemia therapy that did not include concomitant steroid therapy. Our retrospective analysis indicates that IV administration of pegylated ASNase increases the incidence of low-grade, but not grade 3-4, hypersensitivity reactions compared with IM administration.

Key Words: ALL, pegasparaginase, hypersensitivity, adverse reactions

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Asparaginase (ASNase) was first discovered to be a chemotherapeutic agent in 1961 and introduced in clinical trials in the 1970s.^{1,2} It has significantly improved the event-free survival and overall survival in both children and adult patients with acute lymphoblastic leukemia (ALL).^{3,4} The benefit of the drug is dependent on adequate ASNase dosing, and its removal due to toxicity jeopardizes its therapeutic effects.³ ASNase is an enzyme that breaks down asparagine into aspartic acid and ammonia. Leukemia cells lack asparagine synthetase and are incapable of synthesizing asparagine de novo. Consequently, asparagine depletion results in nutritional deprivation, inhibition of protein synthesis, and apoptotic cell death in lymphoblasts.⁴

Multiple side effects have been reported with the use of ASNase, the most common being hypersensitivity reactions that can be seen in up to 30% of patients.⁵ Other adverse

effects include: thrombotic events, hyperglycemia, pancreatitis, hypertriglyceridemia, and hyperammonemic encephalopathy.^{6–10} ASNase is a foreign protein and consequently immunogenic; hence, the mechanism of hypersensitivity reaction is linked to neutralizing anti-ASNase antibodies that can form with or without (silent hypersensitivity) an associated clinical allergic reaction. These antibodies alter the pharmacokinetics and bioavailability of the drug and are associated with inferior outcomes even in those with silent hypersensitivities.^{11–13}

There are 3 preparations of ASNase, 2 of which are unmodified forms from bacterial sources. L-ASNase is derived from the native *Escherichia coli* enzyme, and *Erwinia* ASNase is purified from *Erwinia chrysanthemi*. The third formulation is pegylated ASNase (pegASNase), which is a chemically modified form of *E. coli* ASNase produced by conjugating the original enzyme to polyethylene glycol.^{14–16} Although ASNase's mechanism of action is unaffected by the form it is in, the formulations differ in pharmacokinetic properties and their tendency to produce adverse effects. Native *E. coli* L-ASNase has a half-life of 26 to 30 hours and is historically associated with a higher incidence of adverse effects. This form is no longer available in the United States.¹⁵ *Erwinia* ASNase has the shortest half-life of all 3 forms (~ 16 h). It is also associated with fewer incidents of hypersensitivity reactions.¹⁵ However, it showed inferior outcomes when compared with native *E. coli* L-ASNase in a European randomized control trial, though the dosing regimen used during the trial (10,000 IU/m² twice weekly) was less than that used in current treatment regimens (25,000 IU/m² Monday/Wednesday/Friday), which may account for the inferior outcomes.¹⁷

PegASNase is the most recently developed commercial formulation. Conjugating the PEG molecule to L-ASNase alters the immunogenicity of the protein and increases its

TABLE 1. Characteristics of the Patients and Their Disease

Characteristics	Number
Demographics	
Male (IV/IM)	44 (13/31)
Female (IV/IM)	47 (18/29)
Age (y)	0-19 (median 7.1)
Diagnosis	
HR B-cell ALL (IV/IM)	32 (15/17)
SR/LR B-cell ALL (IV/IM)	46 (12/34)
T-cell ALL	11 (4/7)
Other	2 (1/1)

ALL indicates acute lymphoblastic leukemia; HR, high risk; IM, intramuscular; IV, intravenous; LR, low risk; SR, standard risk.

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TABLE 2. Summary of Patients With Allergic Reactions: A. IM B. IV

Treatment Protocol		Age (y) and Sex	Body Surface Area (m ²)	BMI (% for age)	No. Doses Before Reacting	No. IM Injections	Concomitant Steroid ALL Therapy	Type and Grade of Allergic Reaction*	Treatment of Allergic Reaction	Switch to <i>Erwinia</i> ASNase
A. IM Form										
1	AALL-0232	10 M	1.33	82	2	3	None	Grade III anaphylaxis	Diphenhydramine, hydrocortisone	Yes
2	AALL-0331	7 F	0.95	79	1	2	None	Grade III anaphylaxis	Diphenhydramine, hydrocortisone	No, omitted
3	AALL-0331	1 M	0.5	98	1	1	None	Grade II allergic reaction	Diphenhydramine, hydrocortisone	No, omitted
4	AALL-0331	5 M	0.8	75	1	2	None	Grade III anaphylaxis	Diphenhydramine, hydrocortisone	No, omitted
5	AALL-0232	6 F	0.87	93	1	2	None	Grade III anaphylaxis	Diphenhydramine, hydrocortisone	Yes
6	AALL-0331	6 M	0.85	79	2	2	None	Grade IV anaphylaxis	Diphenhydramine, hydrocortisone, salbutamol, epinephrine	Yes
7	AALL-0232	11 M	1.26	85	2	3	None	Grade III anaphylaxis	Diphenhydramine, hydrocortisone	Yes
8	POG 9906	9 M	1.1	44	2	2	None	Grade III anaphylaxis	Diphenhydramine, hydrocortisone	No further scheduled doses
B. IV Form										
1	AALL-1131	2 F	0.6	55	2	None	Grade III anaphylaxis	Diphenhydramine, hydrocortisone	Yes	
2	AALL-1131	1 F	0.55	47	2	None	Grade II allergic reaction	Diphenhydramine, hydrocortisone	No, successfully rechallenged with pegASNase	
3	AALL-0932	4 F	0.68	57	1	Dexamethasone	Grade III anaphylaxis	Diphenhydramine, hydrocortisone	No further scheduled doses	
4	AALL-0434	6 F	0.87	62	2	None	Grade II allergic reaction	Diphenhydramine, hydrocortisone	Yes	
5	AALL-0434	13 M	1.32	35	1	None	Grade III anaphylaxis	Diphenhydramine, hydrocortisone	Yes	
6	AALL-1131	7 F	0.97	85	2	None	Grade II allergic reaction	Diphenhydramine, hydrocortisone	Yes	
7	AALL-1131	7 M	0.9	69	2	None	Grade III anaphylaxis	Diphenhydramine, hydrocortisone	Yes	
8	AALL-1131	8 F	1	26	2	None	Grade III anaphylaxis	Diphenhydramine, hydrocortisone	Yes	
9	AALL-0932	1 M	0.6	42	1	Dexamethasone	Grade III anaphylaxis	Diphenhydramine, hydrocortisone	No further scheduled doses	
10	AALL-0932	2 M	0.65	19	1	Dexamethasone	Grade II allergic reaction	Diphenhydramine, hydrocortisone	No further scheduled doses	

*Graded according to CTCAE 4.03, 2010.

ALL indicates acute lymphoblastic leukemia; ASNase, asparaginase; BMI, body mass index; F, female; IM, intramuscular; IV, intravenous; M, male.

plasma circulation time. The half-life of pegASNaSe is 5.5 to 7 days, and this prolonged $t_{1/2}$ allows for a single administration of pegASNaSe compared with several injections of the unpegylated formulations. Avramis et al¹² performed a randomized control trial in which 118 standard risk ALL patients were randomly assigned to receive native ASNaSe or pegASNaSe during induction and delayed intensification. Both groups had a similar incidence of adverse events and a similar event-free survival early in the study. However, the response to induction therapy was faster and remission was achieved sooner with pegASNaSe.

For years, pegASNaSe could only be administered intramuscularly (IM) as it was the only formulation available. With the subsequent availability of intravenous (IV) administration, we suspect that we have had an increase in the incidence of hypersensitivity reactions in our practice. We, therefore, investigated the hypothesis that the incidence of adverse reactions is greater when pegASNaSe is administered IV compared with IM.

MATERIALS AND METHODS

After obtaining Institutional Review Board approval, we retrospectively reviewed the medical records of ALL patients who were treated between 2003 and 2013 at either of our 2 cancer centers: Women and Children's Hospital of Buffalo (WCHOB) and Roswell Park Cancer Institute (RPCI). Both newly diagnosed and relapsed patients were included. We identified the episodes of adverse reactions with the administration of pegASNaSe and compared the prevalence in each route of administration (IV vs. IM). The severity of reaction was recorded according to Common Terminology Criteria for Adverse Events (CTCAE 4.03, 2010).

The dose of pegASNaSe was 2500 IU/m². In our practice, the IM pegASNaSe is administered with a total volume not exceeding 2 mL at a single injection site. With a dosing concentration of 750 IU/mL, multiple IM injections are often required, ranging from 1 to 3 depending on the patient's calculated body surface area (Table 2). For IV administration, the total pegASNaSe dose is diluted in 100 mL of NS or D5W and infused over 1 to 2 hours through a NS or D5W running infusion line. We observe patients for at least 1 hour after administration for signs of hypersensitivity.

We performed a χ^2 analysis to compare the relative risk of allergic events with IV dosing compared with IM, using GraphPad PRISM 6 (San Diego, CA).

RESULTS

We identified 96 pediatric patients with ALL who were treated with pegASNaSe at WCHOB and RPCI between 2003 and 2013. Five patients who received both IV and IM forms were excluded. The remaining 91 patients were included in the final analysis. Forty-six patients were treated for standard-risk or low-risk ALL, 32 for high risk, 11 for T-cell ALL, 1 for Ph + ALL, and 1 for infant ALL (Table 1).

Thirty-one patients received IV pegASNaSe, whereas 60 received the IM form. A total of 18 patients experienced at least 1 allergic event attributed to pegASNaSe (Table 2). None of the patients reacted to pegASNaSe during their first exposure. This may be related to the lack of immunotolerance within the first exposure and concomitant steroid use during induction phase doses of pegASNaSe. The

overall incidence of grade II or higher hypersensitivity reactions was 32.2% (N = 10) in the IV pegASNaSe group and 13.3% (N = 8) in the IM group. There was no significant difference in the rates of reaction between sexes, though there was a trend toward more reactions in high-risk ALL patients (Table 3). There was no significant difference in the incidence of hypersensitivity reactions between our 2 practice locations.

There was an increase in hypersensitivity reactions of any grade in the IV versus IM form. The relative risk of a hypersensitivity reaction when pegASNaSe is given IV compared with IM was 2.42 (95% CI, 1.06-5.51; $P = 0.032$), when any grade ≥ 2 reaction is included. However, when only grade 3 and 4 reactions were analyzed, we found that the rates of reactions were similar between IV (19.4%) versus IM (11.7%) groups (Table 4). As expected, most hypersensitivity reactions occurred during periods without concomitant corticosteroid therapy (Table 4).

DISCUSSION

ASNaSe is a crucial backbone component in the treatment of childhood ALL. Multiple randomized control trials have demonstrated superior outcomes when adding ASNaSe to the treatment regimen.^{18,19} Pegylating the ASNaSe modifies the immunogenicity of the original drug and is associated with less adverse events.¹² PegASNaSe could be administered either IV or IM with recent deviation toward the IV form as it minimizes the anxiety and pain associated with IM injections, which in most patients are multiple and may be as many as 6 injections in obese patients.⁴ When the ASNaSe is administered during a phase of ALL therapy that includes corticosteroid therapy, usually daily oral prednisone or dexamethasone started several days before the ASNaSe dose, the rate of allergic reaction is substantially reduced.²⁰

Published information pertaining to the clinical experience with IV pegASNaSe in pediatric patients is limited to a few trials comparing the IV form to the IM in terms of the incidence of adverse events, pharmacokinetics, and long-term outcomes. The first report comparing the incidence of allergic reaction using IV versus IM route of ASNaSe was reported by Nesbit et al²¹ in 1979. This study demonstrated

TABLE 3. The Incidence of CTCAE 4.03 Grade ≥ 2 Hypersensitivity Reactions Divided by Sex and Risk Groups

	Reacted/Total (IV%)	Reacted/Total (IM%)
Male	4/13 (30.7)	6/32 (18.8)
Grade II	1/13 (7.8)	1/32 (3.1)
Grade III-IV	3/13 (23)	5/32 (15.6)
Female	6/18 (33.3)	2/28 (7.1)
Grade II	3/18 (16.7)	0/28 (0)
Grade III-IV	3/18 (16.7)	2/28 (7.1)
SR B-cell ALL	3/12 (25)	4/34 (11.8)
Grade II	1/12 (8.3)	1/34 (2.9)
Grade III-IV	2/12 (16.7)	3/34 (8.8)
HR B-cell ALL	5/15 (33.3)	4/17 (23.5)
Grade II	2/15 (13.3)	0/17 (0)
Grade III-IV	3/15 (20)	4/17 (23.5)
T-cell ALL	2/4 (50)	0/7 (0)
Grade II	1/4 (25)	0/7 (0)
Grade III-IV	1/4 (25)	0/7 (0)

ALL indicates acute lymphoblastic leukemia; HR, high risk; IM, intramuscular; IV, intravenous; SR, standard risk.

TABLE 4. Hypersensitivity Reactions Following PegASNa by Grade and Concomitant Steroid Therapy

	Concomitant Steroid Therapy	Doses Before Reacting	Allergic or Anaphylactic Reaction Grade (CTCAE v4.03)				Any Reaction > Grade 1 (%)	Grade ≥ 3 or Anaphylactic (%)
			2	3	4	5		
IV	Yes	1	1	2	0	0	9.8	6.5
	No	1.9	3	4	0	0	22.6	12.9
IM	Yes	0	0	0	0	0	0	0
	No	1.5	1	6	1	0	13.3	11.7

IM indicates intramuscular; IV, intravenous.

that the IM method of administering L-ASNase is as effective, but less toxic than the IV method for children with advanced ALL.

August et al²² conducted a retrospective review comparing the incidence of hypersensitivity reactions to pegASNa in 68 children when administered by IM or IV routes. Although the study showed a slight increase in the incidence of hypersensitivity reactions with IV administration, the difference was not statistically significant possibly related to lack of power from the relatively small sample size.

A similar study conducted by Pidaparti and Bostrom²³ revealed a higher incidence of allergic reactions in the IV group compared with IM (36% vs. 9%), though there were only 11 patients in the IV group. The observed incidence was higher in high-risk patients (16%) versus standard risk (6%) likely related to a higher cumulative dose administered in high-risk protocols, similar to the trend noted in our cohort.

More recently, Petersen et al²⁴ retrospectively evaluated 318 ALL patient records. Approximately half of the study group received IV and the other received IM pegASNa. Similar to our study, the incidence of allergic reactions in the IV group (19.5%) was higher compared with the IM group (10.7%) ($P = 0.028$). Unlike our finding that IV pegASNa was associated primarily with low-grade reactions, their analysis suggested a similar grade of reactions between the 2 treatment groups. They did not, however, account for any differences in concomitant steroid therapy administered as part of the phase of ALL therapy.²⁰ One additional confounding factor in such an analysis includes the occurrence of infusion-related reactions that occur with IV, but not IM routes of administration. These infusion reactions are generally low-grade reactions that are not true hypersensitivity reactions and may account for the increased rate of low-grade reactions in our population as it can be difficult to differentiate between an infusion reaction and a low-grade hypersensitivity reaction, especially in our retrospective chart review.

Antibody formation is the major cause of hypersensitivity reactions to ASNase, leading to faster depletion of ASNase and consequently higher serum asparagine levels. The Children's Cancer Group trial (CCG-1961) demonstrated inferior outcomes in patients who developed anti-ASNase antibodies to native *E. coli* ASNase, including those with silent hypersensitivity in which circulating antibodies develop in the absence of clinical evidence of hypersensitivity.²⁵ While our data indicate a possible higher rate of low-grade clinical hypersensitivity reactions with the IV form, we cannot comment on any difference in silent hypersensitivity between the 2 routes of administration as anti-ASNase antibodies were not

assessed in our retrospective review. The rate of silent inactivation is known to be significantly lower with pegASNa than with native ASNase.²⁰ In addition, it is unclear whether patients with signs of low-grade hypersensitivity reactions develop inactivating antibodies and whether these clinical signs are truly representative of immune-mediated hypersensitivity reactions.

Bleyer et al²⁶ suggested guidelines for the clinical application of an ASNase activity assay to evaluate suspected hypersensitivity reactions and/or silent inactivation. These guidelines are designated for patients with clinical allergic reactions, which are commonly associated with neutralizing antibody formation resulting in inadequate ASNase activity. It could also be used to help identify those with possible silent inactivation in which there is low ASNase activity without clinical symptoms.

Some toxicities of ASNase have been noted to occur more often in obese patients (eg, hepatic and pancreatic toxicities).⁴ In our pediatric patients, hypersensitivity reactions were not more frequent in those with an elevated BMI.

Our study suggests a higher rate of low-grade hypersensitivity reactions to pegASNa when given IV. However, the difference was minimal between IV and IM groups when considering only grade 3 and 4 hypersensitivity reactions and the difference in low-grade reactions may be related to the occurrence of infusion-related reactions in patients receiving the IV form. Further studies to evaluate inactivating antibody formation and ASNase activity with routes of administration are warranted based on existing data that the presence of a hypersensitivity reaction may indicate the presence of inactivating antibodies that can compromise the effectiveness of ASNase.

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