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Comparison of hypersensitivity rates to intravenous and intramuscular PEG-asparaginase in children with acute lymphoblastic leukemia: A meta-analysis and systematic review

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Abstract

Background: Pegylated-asparaginase (PEG-ASP) is a critical treatment for pediatric acute lymphoblastic leukemia (ALL) and has traditionally been delivered via intramuscular (IM) injection. In an attempt to reduce pain and anxiety, PEG-ASP has increasingly been delivered via intravenous (IV) administration. The study objective was to perform a meta-analysis and systematic review to compare and generate pooled hypersensitivity rates for IM and IV PEG-ASP.

Methods: A systematic literature search was conducted for all epidemiological studies that investigated IV and IM hypersensitivity rates for pediatric ALL. Included studies were critically appraised using the GRACE checklist. Pooled estimates and odds ratios with 95% confidence intervals (CIs) for IM and IV hypersensitivity rates were derived based on either a random or fixed effects model.

Results: Four studies satisfied the inclusion criteria and were of adequate quality. The random effects pooled hypersensitivity rates were 23.5% (95% CI 14.7–33.7) and 8.7% (95% CI 5.4–12.8) for IV and IM, respectively. The fixed effects pooled odds ratio after adjusting for publication bias was 2.49 (95% CI 1.62–3.83), indicating a significantly higher risk of hypersensitivity for IV over IM PEG-ASP. This risk is far more pronounced for high-risk (HR) patients compared with standard-risk (SR) patients (IV vs. IM: HR ↑35.2% and SR ↓2.9%).

Conclusions: Although administering PEG-ASP through IV is preferable for patients, it poses a significantly higher risk of hypersensitivity when compared with IM administration, especially for HR patients. We recommend pediatric oncologists consider treating patients with HR pediatric ALL with IM PEG-ASP to reduce the risk of hypersensitivity.

KEYWORDS

acute lymphoblastic leukemia, hypersensitivity, intramuscular, intravenous, meta-analysis, PEG-asparaginase

1 | INTRODUCTION

Asparaginase therapy is critical in the treatment of acute lymphoblastic leukemia (ALL).[1–3] Asparaginase is an enzyme that depletes the serum amino acid asparagine, which lymphoblasts rely upon.[4,5] However, the delivery of asparaginase can be highly immunogenic, as it is derived from bacteria.[6,7] Pegylated-asparaginase (PEG-ASP) is associated with a significant drop in hypersensitivity (i.e., allergic) rates,

Abbreviations: ALL, acute lymphoblastic leukemia; B-ALL, B-cell acute lymphoblastic leukemia; CI, confidence interval; CTC, common toxicity criteria; HR, high risk; IM, intramuscular; IV, intravenous; MeSH, Medical Subject Heading; OR, odds ratio; PEG-ASP, pegylated asparaginase; PICO, Patient, Intervention, Comparator, and Outcome; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses; RCT, randomized controlled trial; RevMan, Review Manager; SR, standard risk; T-ALL, T-cell acute lymphoblastic leukemia

but nevertheless pegylation does not completely eliminate immunogenicity.[8] Traditionally, PEG-ASP was administered intramuscularly. However, due to administration challenges, particularly patient anxiety and pain as well as perceived equivalency in efficacy, intravenous (IV) delivery has become the standard of practice among the pediatric oncology community in more recent years.[9,10]

While retrospective studies have compared hypersensitivity rates between intramuscular (IM) and IV administration, rates for IV administration appear to vary significantly in the literature. One study on hypersensitivity reactions for IV administration reported a hypersensitivity rate of 36.4%,[11] while others found rates corresponding to 19.5[10] and 12.5%.[12] For IM, rates have been much more consistent with reported values of 9.2,[11] 10.7,[10] and 11.1%.[12] Based on the existing literature, current evidence points to two possibilities. It may be that there is no difference in hypersensitivity between IV and IM administration[12] or that IV poses a greater risk for hypersensitivity in comparison with IM.[10,11] The objective of this study was to conduct a systematic review and meta-analysis with the aim of comparing hypersensitivity rates to IV and IM PEG-ASP to better inform clinical practice through evidence-based decision-making.

2 | METHODS

2.1 | Literature search

The literature was systematically searched via a comprehensive literature search (full search strategy can be found in the Supplementary Appendix S1). We used MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and CINAHL from inception to 2015 to identify studies that investigated hypersensitivity to PEG-ASP in patients with pediatric ALL. Our search strategy (Supplementary Appendix S1) used text words and relevant indexing to capture the concept of preventing hypersensitivity reactions to PEG-ASP in patients with pediatric ALL. The Patient, Intervention, Comparator, and Outcome (PICO) statement was used to structure the literature search (Supplementary Table S1). We used medical subject heading (MeSH) and text words related to population characteristics (e.g., pediatric, children, ALL, etc.), the intervention and comparator (e.g., PEG-Asparaginase, pegylated asparaginase, intravenous, intramuscular, etc.), and the outcome (e.g., hypersensitivity reaction, hypersensitivity rate, silent antibody formation, etc.). We also assessed the reference lists of included papers for additional relevant studies. We restricted our search to studies published in English while acknowledging our study is prone to language bias and expanded our search to include gray literature sources.

2.2 | Eligibility criteria

Two authors (HH and OS) screened the titles and abstracts independently to identify potentially eligible studies. Discrepancies were jointly reviewed to reach consensus and the principle investigator (KG) was available as an arbitrator. To determine which studies were eligible for review, two authors (HH and OS) independently screened the full text of the identified studies. Studies were deemed eligible if they were epidemiological studies in which the population investigated was children aged 0–18 years, diagnosed and treated for ALL, and outcomes reported included hypersensitivity reactions to PEG-ASP by IV and IM route of administration. Studies were excluded if the study population included patients diagnosed and treated for relapsed ALL, since these patients have considerably poorer outcomes and would introduce bias into the meta-analysis.[13]

2.3 | Data extraction

Two authors (HH and OS) extracted data independently and disagreements were resolved by consensus. The principle investigator (KG) was available as an arbitrator. From each eligible study, we extracted, where available, (i) author, year, and country of publication; and (ii) study population characteristics (age, sex, years of diagnosis, sample size, treatment protocol, risk type at diagnosis, immunophenotype, number of patients who experienced a hypersensitivity reaction by route of administration (IV and IM), hypersensitivity grading scale (e.g., Common Toxicity Criteria [CTC], etc., and phase of treatment that the hypersensitivity reaction occurred).

2.4 | Quality assessment

As there is no standard scale to assess quality in observational studies,[14,15] we used a modified version of the GRACE checklist to perform the critical appraisal of the included studies (Supplementary Table S2).[16]

2.5 | Meta-analysis

A pooled odds ratio (OR) with 95% confidence intervals (CIs) was generated to evaluate the associations between route of PEG-ASP administration and the risk of a hypersensitivity reaction. Pooled estimates and 95% CIs for IM and IV hypersensitivity rates were derived as well as by risk type and allergic grade. Heterogeneity was assessed using the I^2 estimate and the P value of the χ^2-test. Heterogeneity was assumed if the P value was less than 0.10 and I^2 50% or more, in which case, the random effects model was used to analyze the results of the studies. If the P value was more than 0.10 and I^2 less than 50%, homogeneity was assumed and the fixed effects model was used to analyze the result of the studies. Publication bias was assessed using Begg's funnel plot and Egger's test.[17] A P value of less than 0.05 as calculated by Egger's test and asymmetry of Begg's funnel plot was used to define publication bias. If publication bias existed, the trim and fill approach was implemented in order to generate an estimated pooled OR that accounts for unpublished negative findings.[16] A forest plot with each study's included OR as well as the pooled OR along with 95% CIs, with the weight of each OR indicated by the relative size of the study, was used to visualize the range of effects. The robustness of our meta-analysis was assessed by conducting a leave-one-out sensitivity analysis.[18] The meta-analysis was performed using Review Manager (RevMan) version 5.3 (Cochrane's Informatics & Knowledge

Management Department, Copenhagen, Denmark) and adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement. Begg's funnel plot and Egger's test were performed using Comprehensive Meta-Analysis version 2.0 (Biostat Inc., Englewood, USA). Pooled random effects estimates were derived using Stats Direct version 2.7 (Stats Direct Ltd, Cheshire, UK).

2.6 | Estimated financial burden by route of administration

A secondary objective of our study was to provide a crude unadjusted estimate for the financial burden related to route of administration for PEG-ASP for the treatment of pediatric ALL in Canada. A crude national estimate of costs by route of administration was calculated for the treatment of pediatric ALL based on the average annual caseload in Canada (262 cases)[2,3,19] and unadjusted hypersensitivity rates found from the meta-analysis. The cost per case if a hypersensitivity reaction occurs or does not occur was based on a study conducted by Tong et al.[20] and assumed to be $113,558 and 57,893 respectively.

3 | RESULTS

3.1 | Included studies

Our search identified 263 studies from MEDLINE, EMBASE, CINAHL, and Cochrane. After screening titles and abstracts, 13 studies were considered potentially eligible and were retrieved for full text review. Of these, nine (Supplementary Appendix S1) studies were excluded and four[10,11,21,22] were included in this meta-analysis and systematic review that reported results on 752 patients with pediatric ALL (Fig. 1). Table 1 summarizes the characteristics of the four studies, and reasons for exclusions can be found in Figure 1.

3.2 | Meta-analysis

All included studies provided hypersensitivity rates for patients stratified by IV and IM routes of administration. The random effects hypersensitivity rates were 23.5% (95% CI 14.7–33.7) and 8.7% (95% CI 5.4–12.8) for IV and IM, respectively. The random effects pooled hypersensitivity rates based on the MacDonald et al. (2014)[22] and Pidaparti and Bostrom (2012)[11] studies were 2.5% (95% CI 0.2–12.5) and 19.1% (95% CI 12.7–26.4) for patients with standard risk (SR) and high risk (HR) ALL, respectively. Heterogeneity was assumed as *P* values were less than 0.10 and I^2 estimates 50% or more. Random effects pooled hypersensitivity rates by risk type and allergic grading scale are summarized in Tables 2 and 3, respectively.

Odds ratios were computed for each study and the pooled fixed effects OR, unadjusted for publication bias, was 2.99 (95% CI 1.86–4.80) (Fig. 2). Homogeneity was assumed as the I^2 estimate was 13% and the *P* value was 0.33. The random effects model was also applied, which unadjusted for publication bias generated a pooled OR of 3.15 (95% CI 1.85–5.37).

3.3 | Publication bias

A *P* value of 0.04 was calculated by Egger's test, indicating the presence of publication bias. The initial funnel plot displayed asymmetry, also indicating publication bias. The trim and fill approach was applied to generate an estimated pooled fixed effects OR of 2.49 (95% CI 1.62–3.83) (Fig. 3). The trim and fill approach was also applied to the random effects model and generated a pooled OR of 2.57 (95% CI 1.51–4.38).

3.4 | Sensitivity analysis

To evaluate the robustness of the study, we performed a leave-one-out sensitivity analysis by iteratively removing one study at a time and recalculating the summary OR.[18] The analysis revealed that our results were not driven by any single study with the ORs remaining stable.

3.5 | Quality assessment

Treatment and primary outcome information was adequately recorded in all studies. The primary clinical outcomes were measured objectively and validated in all but one study for which not enough information was available. Hypersensitivity rates were measured equally between groups in all four studies and the known confounder of risk type was recorded in three studies. Age was included in the study that did not report risk type, which can be used to partially derive risk type based on the National Cancer Institute/Rome criteria (SR = age $\geq$1 year and <10 years, and white blood cell count $<50 \times 10^9$ l^{-1}).[23] All studies restricted their population to patients who were new initiators to treatment. Three studies used concurrent comparators and the remaining study used a historical comparison group without justification. Three studies took risk into account for analysis and all studies were free of immortal time bias. None of the studies conducted analysis to test assumptions on which primary results are based. Overall, the included studies were of adequate quality. A summary of the quality assessment completed according to the GRACE checklist can be found in Supplementary Table S2.

3.6 | Estimated cost due to hypersensitivity by route of administration

The estimated annual financial burden in Canada for patients with and without hypersensitivity treated with IM PEG-ASP was found to be $2.6 million and $13.8 million, respectively, and for those treated with IV PEG-ASP, $7.0 million and $11.6 million, respectively. The estimated annual cost savings if patients were treated solely with IM PEG-ASP when compared with IV PEG-ASP is approximately $4.4 million. Details on cost estimates can be found in Supplementary Table S3.

4 | DISCUSSION

The results of our meta-analysis revealed that the pooled estimate for hypersensitivity from IV PEG-ASP was 23.5% (95% CI 14.7–33.7) and significantly higher than IM PEG-ASP, which was 8.7% (95% CI 5.4–12.8). Patients treated with IV PEG-ASP are more than

TABLE 1 Characteristics of included studies

Study	Study design	Sample size	Study population years	Sex	Mean/median age	Immunophenotype	Risk type by route of administration	Country	Allergic rate by route of administration		Findings
									IV (n, %)	IM (n, %)	
Petersen (2014)	Retrospective chart review	Total: 318 IV: 159 IM 159	2006–2011	IV: 76 F 83 M IM: 68 F 91 M	Median age (IQR): 5.5 (3.2 – 11.3) years	IV: 142 B-ALL 13 T-ALL 4 Mixed lineage ALL IM: 138 B-ALL 20 T-ALL 1 Mixed lineage ALL	N/A	USA	31 (19.5%)	17 (10.7%)	Significantly higher hypersensitivity rate for IV vs. IM PEG-ASP(P = 0.028) and by sex (P = 0.006) No difference in reaction severity between IV and IM (P = 0.862); all reactions CTCAE grade 2 (75 %) to 3 (25 %) Onset of allergy significantly faster in IV patients compared to IM (P < 0.001) Factors not significantly associated with increased reaction risk: Age and immunophenotype
MacDonald (2014)	Retrospective chart review	Total: 128 IV: 51 IM: 77	2005–2011 for IM and 2011–2013 IV	N/A	N/A	N/A	IV: 35 SR 16 HR IM: 55 SR 22 HR	Canada	7 (13.8%)	2 (2.6%)	Significantly higher allergic rate for IV vs. IM PEG-ASP (P = 0.029) Significantly higher rate of allergy in HR-ALL than SR-ALL patients(P = 0.0001) Significantly higher allergic rate for IV PEG-ASP vs. IM PEG-ASP in HR-ALL (P = 0.021)
Abbott (2015)	Retrospective chart review	Total: 109 IV: 40 IM: 69	2010–2012	IV: 19 F 21 M IM: 30 F 39 M	Mean age (range) Total: 5.9 (0.03–17.4) IV: 6.2 (0.6–16.9) IM: 5.7 (0.03–17.4)	N/A	N/A	Canada	14 (35.0%)	8 (11.6%)	Significantly higher rate of allergy for IV patients over IM (P = 0.005) and for HR-ALL patients over SR-ALL (0.012). High risk defined as (Other = high-risk and very high risk acute lymphoblastic leukemia, infant acute lymphoblastic leukemia, T-ALL, and non-Hodgkin lymphoma) No difference in reaction severity between IM and IV groups (P = 0.11) Factors not associated with increased reaction risk: age, sex, and immunophenotype
Pidaparti (2012)	Retrospective chart review	Total: 197 IV: 11 IM: 186	2005–2010	N/A	N/A	N/A	IV: 4 SR 7 HR IM: 108 SR 78 HR	USA	4 (36.4%)	17 (9.1%)	Significant higher rate of allergy for IV vs. IM PEG-ASP (P = 0.019) Significantly higher rate of allergy in HR-ALL vs. SR-ALL (P = 0.034) Mean Common Toxicity Criteria 4.0 allergic grade was significantly lower (P value = 0.007) for IV PEG-ASP compared to IM PEG-ASP. Factors not associated with increased reaction risk: sex and immunophenotype

Table adapted from Table 4 of Abbot (2015) study. CTCAE, Common Terminology Criteria for Adverse Events; F, female; HR-ALL, high-risk acute lymphoblastic leukemia; M, male; SR-ALL, standard-risk acute lymphoblastic leukemia; N/A, not available.

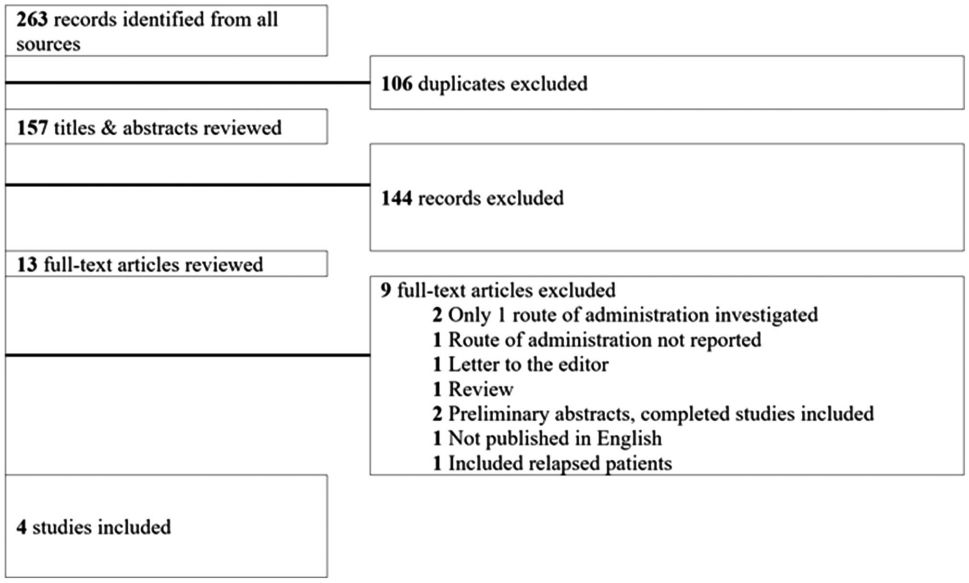

FIGURE 1 Flow diagram of the study selection process

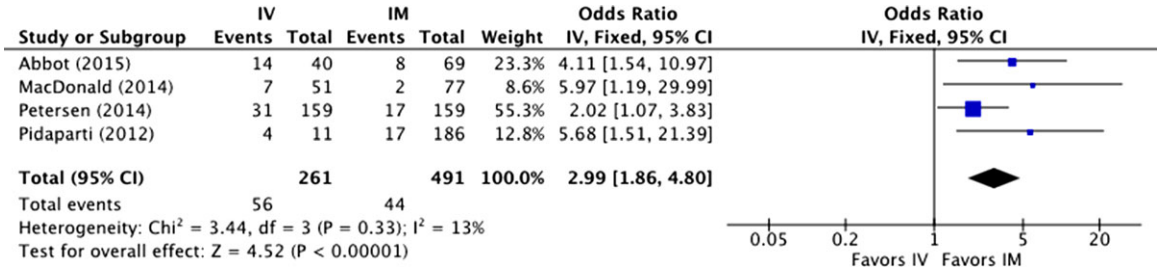

FIGURE 2 Forest plot of hypersensitivity rates for IV versus IM route of administration of PEG-ASP for the treatment of pediatric ALL

TABLE 2 Summary of pooled estimates for hypersensitivity rates by risk type and route of administration

			Standard risk (SR)			High risk (HR)		
Route of administration	SR patients (n)	HR patients (n)	Estimate	95% CI		Estimate	95% CI	
Intramuscular	163	100	2.9%	0.0%	12.8%	12.7%	7.0%	19.9%
Intravenous	39	23	0.0%	N/A		47.9%	28.6%	67.5%

Data based on MacDonald (2014) and Pidaparti (2012) studies, as only these provided allergic rates stratified by risk type and route of administration. N/A, not applicable.

TABLE 3 Summary of pooled estimates for hypersensitivity reactions by grade and route of administration

Route of		Grade 1			Grade 2			Grade 3			Grade 4		
administration	Patients (n)	Estimate	95% CI		Estimate	95% CI		Estimate	95% CI		Estimate	95% CI	
Intramuscular	42	5.3%	0.4%	15.3%	46.6%	16.0%	78.8%	44.3%	23.2%	66.5%	3.8%	0.2%	11.5%
Intravenous	49	0.0%	N/A		74.9%	62.2%	85.8%	25.1%	14.2%	37.8%	0.0%	N/A	

Data based on Abbot (2015), Petersen (2014), and Pidaparti (2012) studies, as only these provided grade of hypersensitivity reaction. N/A, not applicable.

two times as likely to experience a hypersensitivity reaction compared with patients treated with IM PEG-ASP (pooled OR 2.49, 95% CI 1.62–3.83). These results have implications for treatment outcomes and costs. The total cost of a pediatric patient treated for ALL without hypersensitivity to PEG-ASP is estimated to be $57,893.[20] However, if a patient experiences hypersensitivity to PEG-ASP, a switch to *Erwinia* asparaginase is required and this results in a near doubling of the costs ($113,558).[20]

We estimate that based on the pooled hypersensitivity rates in our study and not accounting for risk type, if the pediatric oncology community in Canada was to treat patients with pediatric ALL with IM PEG-ASP, the healthcare system could save approximately $4.4 million annually (Supplementary Table S3). These costs pose a significant burden to hospital budgets and, therefore, reducing the risk of hypersensitivity reactions is critical to minimize financial burden on the healthcare system and adverse patient outcomes.

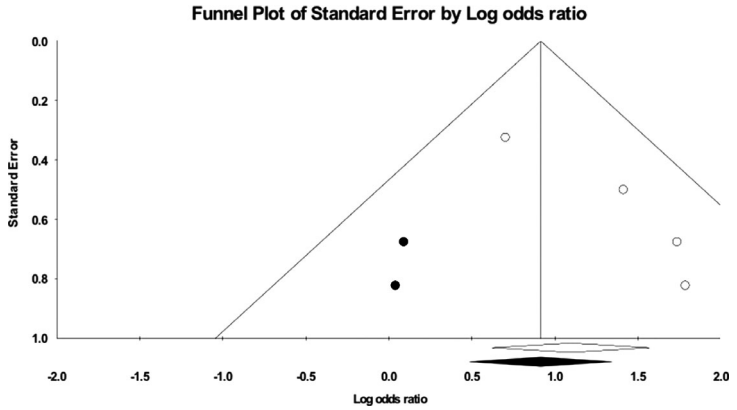

FIGURE 3 Adjusted funnel plot following adjustment for publication bias using the trim and fill approach

Overall, our results indicate that patients with HR-ALL are at higher risk than those with SR-ALL. However, when analyzing these results by route of administration, we found that IV PEG-ASP is suitable for patients diagnosed with SR-ALL as these patients have a low risk of hypersensitivity. On the other hand, for patients diagnosed with HR-ALL, IV PEG resulted in a 35% significant increase in the probability of hypersensitivity when compared with IM PEG (IM: 12.7%, 95% CI 7.0–19.9; IV: 47.9%, 95% CI 28.6–67.5). These results should be interpreted with caution due to low power in the IM groups, as the SR group only had 39 and 163 patients, while the HR group had 23 and 100 patients for the IV and IM groups, respectively.

This increased risk is most likely attributable to the fact that most HR-ALL protocols require the administration of more doses of PEG-ASP than SR-ALL protocols as opposed to actual ALL risk category.[21] Additionally, the timing of the doses differs between the protocols as well as the use of concurrent chemotherapy or corticosteroid therapy, which could potentially explain the variation in hypersensitivity rates.[21] Although the majority of treatment protocols administer PEG-ASP as first line of treatment, PEG-ASP is still delivered as a second line of treatment following hypersensitivity to first-line treatment with native *Escherichia coli* asparaginase in a minority of protocols.[24] However, using PEG-ASP as a second line of treatment in patients hypersensitive to native *E. coli* asparaginase is not optimal because of the possibility of antibodies to native *E. coli* asparaginase cross-reacting with PEG-ASP and thus it is recommended that *Erwinia* asparaginase be used as second line of treatment instead.[24–26] Hypersensitivity to PEG-ASP will vary depending on whether PEG-ASP was administered as first or second line of treatment. None of the studies included in our meta-analysis provided information on whether PEG-ASP was used as a first or second line of treatment. However, this is not expected to impact our results, as our studies were based in North America, where the majority of protocols administer PEG-ASP as first line of treatment.[24]

Our results estimate that the majority of patients who experience a hypersensitivity reaction following IM PEG-ASP will experience grade 2 (*Moderate*) or 3 reactions (*Severe or medically significant but not immediately life threatening*), while the majority of those treated with IV PEG-ASP experience grade 2 reactions. However, these findings were not statistically significant. The weight of this conclusion must be considered with caution, as the precision of the IM and IV PEG-ASP grade estimates are low, given the wideness and overlap of the CIs. Furthermore, the grading of a hypersensitivity reaction relies on a tool that has components prone to subjective bias.

It is unclear what the physiological cause is of the observed difference between IV- and IM-administered PEG-ASP. Pharmacologically, there is no difference between IV and IM PEG-ASP. It has been suggested that differences in immunogenicity could come about from differential handling of the IV-administered drug such as agitation of vials, flow through IV tubing, or dilution with normal saline as well as just differences in how the immune system processes the drugs when delivered through these two different routes.[10] Further research is needed to elucidate the underlying physiological explanation.

This meta-analysis provides a comprehensive estimate of the difference in hypersensitivity rates between IM and IV PEG-ASP for patients with nonrelapsed pediatric ALL based on the existing literature. In total, this study examined 752 patients with ALL, which allows for substantially more statistical power and precision. However, we acknowledge that there are some limitations to our study. The quality of our study is highly dependent on the quality of the included studies.[27] One source of concern is selection bias in the Petersen et al. study, which, unlike the other three studies, did not report on controlling for risk type. If this is not balanced between groups, it could confound the results.[27] Interestingly, this study had a substantially lower OR compared with the three other studies included in our meta-analysis. A point of weakness inherent to the retrospective design of included studies is a lack of standardization across studies in terms of charting protocol.[27] The existing literature and therefore our review is composed entirely of retrospective chart reviews. There may have been inherent differences between patients included in our study that may have influenced the decision for whether a patient should receive IV PEG-ASP or IM PEG-ASP. Inclusion of randomized controlled trials (RCTs) would allow for increased confidence in our findings, as these studies have higher internal validity.[27] In particular, randomization would allow for better minimization of residual confounders.[27] Our study has taken steps to address the key methodological concerns for meta-analyses by including tests for publication bias, including a sensitivity analysis and strictly following through on an a priori design of study protocol.[27]

The majority of relatively recent published RCTs conducted in Europe and North America administered IM PEG-ASP.[28–35] A recently (2015) published RCT (DFC 005-01) by Place et al.[35] compared hypersensitivity and outcomes between patients treated with IM native *E. coli* asparaginase and IV PEG-ASP. They found that 20.3% (47 of 232) and 22.1% (51 of 231) of patients treated with IM native *E. coli* asparaginase and IV PEG-ASP, respectively, experienced hypersensitivity.[35] These results provide strength to our findings as a previous trial (DCOG ALL-9),[36] which administered native IV native *E. coli* asparaginase, found a hypersensitivity rate of 65%, while the published trial by Place et al.[35] found a hypersensitivity rate of 20% for IM native *E. coli* asparaginase. These results demonstrate administering native *E. coli* asparaginase via IM is associated with lower hypersensitivity than administering IV. Our pooled hypersensitivity rates for IM PEG-ASP (8.7%) and IV PEG-ASP (23.5%) are in line with the IM PEG-ASP hypersensitivity rate reported in the NOPHO ALL2008 (12.8%) trial[28] and the IV PEG-ASP hypersensitivity rate reported in DFCI 05-001 (22.1%) trial.[35]

It is important to note that our study investigated clinically overt hypersensitivity reactions and thus did not account for silent hypersensitivity, which is positivity to antibodies for PEG-ASP in the absence of clinically overt hypersensitivity.[37] Patients with silent hypersensitivity often have poorer outcomes as compared with patients with clinically overt hypersensitivity due to the fact that these patients are switched to alternative asparaginase agents, while silent hypersensitivity patients often are not.[33,38] Tong et al.[37] demonstrated that seven (8%) of 89 patients treated with IV PEG-ASP experienced silent hypersensitivity, while Liu et al.[39] showed that 47 (55%) of 85 treated with IM PEG-ASP experienced silent hypersensitivity. Therefore, although IM PEG-ASP accounted for a significantly lower hypersensitivity rate compared with IV PEG-ASP in our study, this difference does not account for the potential that there is a higher probability that patients treated with IM PEG-ASP will experience silent hypersensitivity compared with those treated with IV PEG-ASP. Physicians should practice therapeutic drug monitoring in order to individualize asparaginase therapy.

Our meta-analysis indicates there is a decreased risk of hypersensitivity if PEG-ASP is delivered using the IM route as opposed to IV in pediatric patients diagnosed with ALL. This risk is far more pronounced when taking risk type into consideration, with HR pediatric ALL being associated with a significantly higher risk than SR pediatric ALL for IV PEG-ASP. The implementation of IM PEG-ASP in patients diagnosed with HR pediatric ALL could potentially reduce the risk of a hypersensitivity reaction and hence improve treatment outcomes as well as result in significant cost savings for the healthcare system. The findings of our study warrant validation in larger controlled studies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

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