ALL-576

Systematic Literature Review and Network Meta-Analyses of Hypersensitivity in Patients Receiving Asparaginase Treatment

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Objective

- To evaluate the prevalence and effectiveness of management practices for asparaginase hypersensitivity

Conclusions

- In the SLR, the HSR rate for asparaginase in the first-line setting for patients with ALL/LBL ranged from 6.2 to 28.4% across 4 asparaginase formulations; however, when restricted to comparative studies, NMA 1 (29 studies) showed no significant differences
- In the SLR, recurrent HSR rates following switching varied across the asparaginase formulations with an incidence of 4.2 to 27.3%, and 10.1% with *ERW*-ASP
- NMA 2 (10 studies) showed there was insufficient evidence and a lack of larger randomized control trials to demonstrate a reduction in asparaginase-associated HSRs following premedication or desensitization treatment
- Results should be interpreted with caution regarding the risk of HSRs with asparaginase in patients with ALL/LBL, due to limited evidence in the different treatment settings
- Limitations included: potential for hypersensitivity to be confused with an infusion reaction without TDM and inconsistency in hypersensitivity diagnosis across institutions, suggesting that reliable evaluation across studies cannot be assumed. Limitations of the NMA include homogeneity, transitivity, and consistency assumptions, low number of studies for pairwise comparisons, and bias in the evaluation
- In summary, these data demonstrate that hypersensitivity risk varied across formulations and there is little evidence of clinical benefit from premedication or desensitization. These reviews are limited by the number and size of underlying studies, in particular calaspargase, despite its first-line setting use; warranting further research

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Introduction

- Asparaginase is critical to acute lymphoblastic leukemia/lymphoblastic lymphoma (ALL/LBL) treatment regimens and survival outcomes.[1] Native L-asparaginase (L-ASP) and native *Erwinia* asparaginase (*ERW*-ASP) were historically used in the US for ALL/LBL. Current options include pegaspargase (PEG-ASP; pediatric/adult patients with first-line ALL or asparaginase hypersensitivity), calaspargase pegol-mknl (CAL-ASP; ALL in patients aged 1 month-21 years), and asparaginase *Erwinia chrysanthemi* (recombinant)-rywn (ALL/LBL in patients aged ⩾1 month with hypersensitivity to *E. coli*-derived asparaginase).[2-5] Since 2022, PEG-ASP has been unavailable to patients <22 years in the US[6]
- The 3 asparaginase formulations have different pharmacokinetic profiles and their half-lives vary greatly: CAL-ASP is 13.4 days, PEG-ASP is 5.3-5.73 days (depending on route of administration), and *ERW*-ASP recombinant-rywn is 0.76 days[6]
- Asparaginase has a unique toxicity profile that includes risk of hypersensitivity.[1,6,7] Of the PEG-ASP recipients, 3-24% experience symptomatic hypersensitivity, i.e., a hypersensitivity reaction (HSR)[1]; whereas 8% experience asymptomatic hypersensitivity, i.e., silent inactivation (SI).[8] Both require therapeutic drug monitoring (TDM)[9]
- Asparaginase treatment completion is associated with improved overall survival and event-free survival, with lower relapse risk[10]; whereas patients who discontinue treatment due to intolerable side effects tend to experience poor outcomes[11]
- Patients who switch to the immunologically distinct *ERW*-ASP complete therapy and maintain survival benefits[12]
- To enable treatment completion and preserve effectiveness, National Comprehensive Cancer Network® guidelines recommend prompt switching to the immunologically distinct *ERW*-ASP in the event of hypersensitivity.[2] While prophylactic premedication and desensitization can be utilized, evidence supporting these protocols to prevent hypersensitivity is limited

Methods

Systematic literature review (SLR)

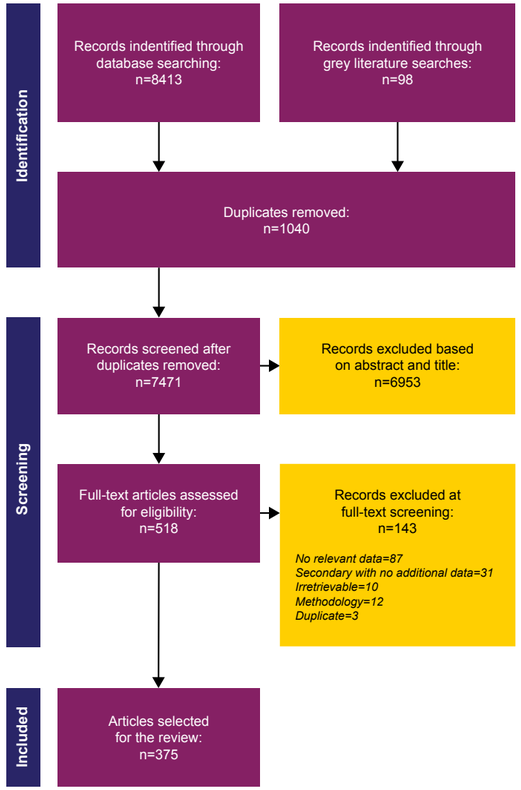
- Results of this SLR conducted between inception and May 2023 were previously presented.[13] Here we provide further updates to September 2025
- The SLR was conducted using Medline, Embase, the Cochrane library, HEORO™, and 8 grey literature sites (conference websites)
  - Studies included: discussed management decisions/practices concerning hypersensitivity prevention or treatment, including SI (author specified or via TDM)
  - Assessment of risk-of-bias (RoB) was via the Cochrane RoB tool (randomized controlled trials),[14] Downs and Black criteria (non-randomized studies),[15] and Drummond criteria (economic models)[16]

Network Meta-Analyses (NMAs)

- Two potential networks were identified using a feasibility study:
  1. HSR following first-line treatment with asparaginase without premedication, by asparaginase type
  2. HSR following first-line treatment with asparaginase, with or without premedication
- The NMAs enabled simultaneous comparisons of ⩾3 treatments across studies. PEG-ASP without premedication was used as the reference treatment
  - Odds ratios (OR) were considered significant if the credible interval (CrI) did not bracket unity (OR=1)
  - Surface under the cumulative ranking (SUCRA) was used as a ranking method

Results

Figure 1. PRISMA Flow of Literature Diagram



PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Systematic Literature Review

- In total 8511 records were identified
  - Of these, 7993 were removed, 518 full-text articles were assessed for eligibility, and 375 studies were included

Table 1. Weighted Mean HSR Rates Across Different Asparaginase Formulations: SLR Results

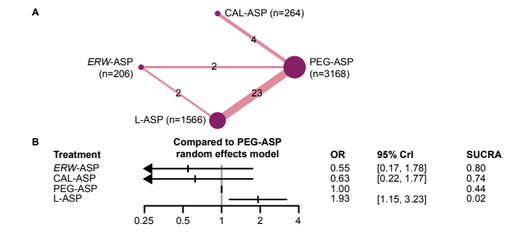
Asparaginase Formulation	Treatment Scenario[a,b]	Weighted Mean HSR Rate (%)	Minimum HSR Rate (%)	Maximum HSR Rate (%)	Total Patients (N)
L-ASP	First-line (no PM)	28.4	0	75.0	15,391
	First-line (prophylactic PM)	18.4	3.8	24.2	217
	Switched to (recurrent HSR)	4.2	4.2	4.2	24
	Rechallenged (PM only)	20.8	0	100	77
	Desensitized (post-HSR)	16.7	0	33.3	6
PEG-ASP	First-line (no PM)	9.9	0	55.1	75,539
	First-line (prophylactic PM)	13.7	1.4	33.3	1182
	Switched to (recurrent HSR)	27.3	0	44.3	213
	Rechallenged (PM only)	9.8	0	41.7	41
	Desensitized (post-HSR)	27.8	19.0	50.0	54
CAL-ASP	First-line (no PM)	18.7	2.7	47.7	667
	First-line (prophylactic PM)	13.8	10.3	19.0	58
	Switched to (recurrent HSR)	0	0	0	1
	Rechallenged (PM only)	-	-	-	0
	Desensitized (post-HSR)	60.0	60.0	60.0	10
ERW-ASP	First-line (no PM)	6.2	5.8	16.7	722
	First-line (prophylactic PM)	-	-	-	0
	Switched to (recurrent HSR)	10.1	0	25.6	586
	Rechallenged (PM only)	-	-	-	0
	Desensitized (post-HSR)	-	-	-	0

[a]First-line data presented for cohorts without prophylactic premedication to align with Network 1 analysis. [b]First-line data includes studies of both newly diagnosed and relapsed/refractory patient populations.
CAL-ASP, calaspargase; *ERW*-ASP, *Erwinia* asparaginase; HSR, hypersensitivity reaction; L-ASP, L-asparaginase; PEG-ASP, pegaspargase; PM, premedication; SLR, systematic literature review.

- The weighted mean rates of HSRs:
  - In the first-line setting, were higher with L-ASP (28.4%), followed by CAL-ASP (18.7%), PEG-ASP (9.9%), and then *ERW*-ASP (6.2%)
  - Following premedication use, were higher with L-ASP (18.4%), followed by CAL-ASP (13.8%), and then PEG-ASP (13.7%). *ERW*-ASP use following premedication was not reported
  - Following switching, were higher with PEG-ASP (27.3%), followed by *ERW*-ASP (10.1%), and then L-ASP (4.2%). Recurrent HSR rate with CAL-ASP was 0% based on 1 patient
  - Following desensitization, were higher with CAL-ASP (60%) and PEG-ASP (27.8%), and lower with L-ASP (16.7%)

Network Meta-Analysis

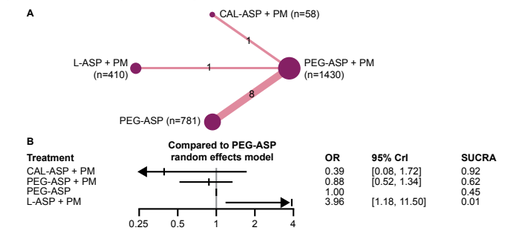
Figure 2. Base Case Analysis of Network 1. (A) NMA 1 examined HSR following first-line treatment with asparaginase without premedication, by asparaginase type (N=29); (B) Forest plot



Note: Numbers on arcs refer to the number of distinct treatment arm comparisons.
CAL-ASP, calaspargase; CrI, credible interval; *ERW*-ASP, *Erwinia* asparaginase; HSR, hypersensitivity reaction; L-ASP, L-asparaginase; NMA, network meta-analysis; OR, odds ratio; PEG-ASP, pegaspargase; SUCRA, surface under the cumulative ranking.

- In NMA 1, 29 studies were identified
  - The observed hypersensitivity risk compared with PEG-ASP was higher with L-ASP (OR 1.93; 95% CrI: 1.15, 3.23), and lower with CAL-ASP (OR 0.63; 95% CrI: 0.22, 1.77) and *ERW*-ASP (OR 0.55; 95% CrI: 0.17, 1.78)
    - No significant differences in risk were observed for *ERW*-ASP or CAL-ASP vs PEG-ASP

Figure 3. Base Case Analysis of Network 2. (A) NMA 2 examined HSRs following first-line treatment with asparaginase, with or without premedication; (B) Forest plot



Note: Numbers on arcs refer to the number of distinct treatment arm comparisons.
CAL-ASP, calaspargase; CrI, credible interval; HSR, hypersensitivity reaction; L-ASP, L-asparaginase; NMA, network meta-analysis; OR, odds ratio; PEG-ASP, pegaspargase; PM, premedication; SUCRA, surface under the cumulative ranking.

- In NMA 2, 10 studies were identified
  - Premedication did not significantly reduce hypersensitivity risk with PEG-ASP (OR 0.88; 95% CrI: 0.52, 1.34) or CAL-ASP (OR 0.39; 95% CrI: 0.08, 1.72)
  - There were no studies identified evaluating premedication use with *ERW*-ASP