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Real-World Asparaginase Use Patterns in Patients With Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma After Recombinant *Erwinia* Asparaginase Approval

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Background

- L-asparaginase (ASP) is a long-standing cornerstone of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) therapies[1]
- While *Escherichia coli (E. coli)* ASPs are typically used as the first ASP, hypersensitivity reactions (HSRs) develop in up to 30% of patients receiving *E. coli* ASPs due to their bacterial origin[2,3]
  - HSRs often lead to treatment discontinuation, which is associated with suboptimal outcomes[2,4]
- Clinical guidelines recommend that patients with HSRs and/or silent inactivation be switched to an immunologically distinct ASP, such as one derived from *Erwinia chrysanthemi*[3,5,6]
- Recombinant *Erwinia* (JZP458, Rylaze®) was approved by the US Food and Drug Administration (FDA) in 2021 as a component of a multi-agent chemotherapeutic regimen for the treatment of ALL/LBL in adult and pediatric patients ⩾1 month old who developed hypersensitivity to *E. coli* ASP[7,8]
- However, there is currently limited published evidence on the use of recombinant *Erwinia* outside of a clinical trial setting

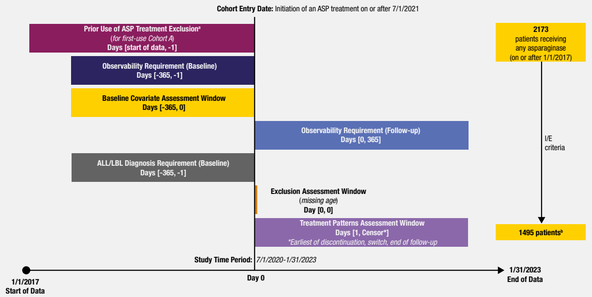
Objective

- To describe treatment patterns and patient characteristics in the US among patients diagnosed with ALL/LBL who initiated an ASP treatment in the post-Rylaze approval timeframe (July 1, 2021-January 31, 2023)

Methods

- This retrospective, non-comparative descriptive analysis involved a de-identified US open claims dataset from Symphony Health including all claims for patients with at least one ALL/LBL-based claim between January 1, 2017 and January 31, 2023 (**Figure 1**)
- Patients in this study population were required to have
  - A diagnosis of ALL/LBL within 365 days prior to the first date of receiving an ASP treatment between July 1, 2021 and January 31, 2023
  - At least 1 medical or pharmacy-based claim 365 days prior to and after the first date of receiving an ASP treatment
- Index date was defined as the first date of receiving an ASP treatment
- Four ASPs were included in this study
  - Two *Erwinia* — recombinant *Erwinia* (Rylaze®) and native *Erwinia* (Erwinaze®)
  - Two *E. coli* — pegaspargase (Oncaspar®) and calaspargase pegol-mknl (Asparlas®)
- There were 2 main cohorts in this analysis
  - Cohort A – patients entered Cohort A when they initiated their first use of ASP
  - Cohort B – a subset of patients in Cohort A who received a second, different ASP
- The cohorts were stratified by ASP formulations received
- Descriptive statistics were reported on the following without statistical comparisons between groups or strata
  - Patient demographic characteristics
  - Distribution of first ASP treatment (Cohort A)
  - Sequence of second ASP treatment (Cohort B)

Figure 1. Study Design



[a]Prior use of ASP treatment exclusion criteria will only apply to Cohort A.

[b]Patients who entered Cohort A.

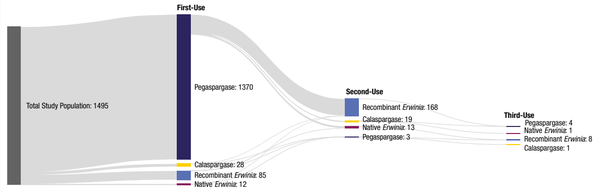
ALL, acute lymphoblastic leukemia; ASP, asparaginase; I/E, inclusion/exclusion; LBL, lymphoblastic lymphoma.

Results

ASP Use Sequence

- The study identified 1398 patients who received an *E. coli* ASP as the first ASP and 97 patients who received an *Erwinia* ASP as the first ASP (Cohort A), including 1370 (91.6%) pegaspargase, 85 (5.7%) recombinant *Erwinia* ASP, 28 (1.9%) calaspargase, and 12 (0.8%) native *Erwinia* ASP-treated patients (**Figure 2**)
- The study identified 203 patients who received a second, different ASP (Cohort B; 13.6% of Cohort A), including 168 (82.8%) recombinant *Erwinia* ASP, 19 (9.4%) calaspargase, 13 (6.4%) native *Erwinia* ASP, and 3 (1.5%) pegaspargase-treated patients
  - Among Cohort B, a small number of patients (n=14) switched ASP treatment a third time
- The most common ASP switch was from pegaspargase to *Erwinia* (n=172, 84.7% of Cohort B), followed by pegaspargase to calaspargase (n=19, 9.4%) and calaspargase to *Erwinia* (n=4, 2.0%)
- Among patients who received an *Erwinia* ASP as the first ASP (n=97), 5.1% switched to another *Erwinia* ASP (4 from native *Erwinia* to recombinant *Erwinia,* and 1 from recombinant *Erwinia* to native *Erwinia*) and 2.1% (n=2) switched to pegaspargase

Figure 2. Real-World ASP Use Pattern in Patients With ALL/LBL



ALL, acute lymphoblastic leukemia; ASP, asparaginase; LBL, lymphoblastic lymphoma.

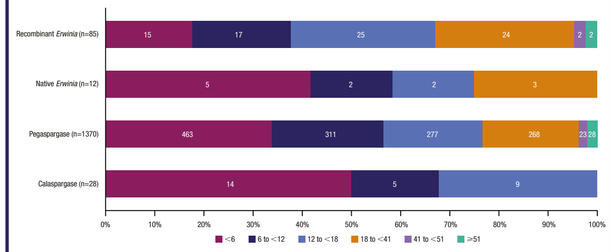
Table 1. Baseline Characteristics

	E. coli ASP		*Erwinia* ASP	
	Cohort A (n=1398)	Cohort B (n=22)	Cohort A (n=97)	Cohort B (n=181)
Age, n (%)				
Mean (SD)	12.8 (11.9)	9.6 (4.7)	15.3 (12.1)	12.5 (9.1)
Median (IQR)	9.0 (4.0, 17.0)	10.0 (4.0, 13.0)	13.0 (7.0, 20.0)	12.0 (5.0, 16.5)
Sex, n (%)				
Male	838 (59.9)	17 (77.3)	65 (67.0)	110 (60.8)
Female	560 (40.1)	5 (22.7)	32 (33.0)	71 (39.2)
Region, n (%)				
Northeast	241 (17.2)	11 (50.0)	25 (25.8)	23 (12.7)
Midwest	276 (19.7)	2 (9.1)	26 (26.8)	39 (21.5)
West	338 (24.2)	4 (18.2)	9 (9.3)	52 (28.7)
South	464 (33.2)	4 (18.2)	33 (34.0)	56 (30.9)
Missing/unknown	79 (5.7)	1 (4.5)	4 (4.1)	11 (6.1)
Number of comorbidities, n (%)[a]				
0	895 (64.0)	11 (50.0)	60 (61.9)	101 (55.8)
1	340 (24.3)	9 (40.9)	25 (25.8)	54 (29.8)
2-4	160 (11.4)	2 (9.1)	12 (12.4)	26 (14.4)
5-9	3 (0.2)	0 (0)	0 (0)	0 (0)
⩾10	0 (0)	0 (0)	0 (0)	0 (0)

[a]Number of comorbidities categories reflect both comorbidities from the Charlson Comorbidity Index and other comorbidities. Malignancy, though a component of the Charlson Index, is not included since all patients have this comorbidity.

ASP, asparaginase; *E. coli, Escherichia coli;* IQR, interquartile range; SD, standard deviation.

Figure 3. Distribution of Patients Using Each Formulation by Age in Cohort A



First-Use ASP (Cohort A)

- Patients in Cohort A had a median age of 10 years, and most were male and living in the South (**Table 1**)
- The median age was lower in the *E. coli* ASP-treated group with a higher percentage of patients aged <6 years, compared to the *Erwinia* ASP-treated group (**Figure 3**)
- Most patients (63.9%, n=955) presented without comorbidities during the baseline period
  - The 3 most common comorbidities at baseline among patients receiving *E. coli* ASPs were obesity (9.8%), chronic obstructive pulmonary disease (9.7%), and liver disease (7.6%)
  - The 3 most common comorbidities in patients receiving recombinant *Erwinia* ASP were obesity (14.1%), liver disease (11.8%), and diabetes (9.4%)
- Distribution of age groups with each ASP formulation is shown in **Figure 3**
  - Among patients aged <18 years (n=1145), 1051 (91.8%), 57 (5.0%), 28 (2.4%), and 9 (0.8%) patients initiated pegaspargase, recombinant *Erwinia* ASP, calaspargase, and native *Erwinia* ASP as their first ASP treatment, respectively
  - Among patients who received *Erwinia* (recombinant and native, n=97), around two-thirds were <18 years old

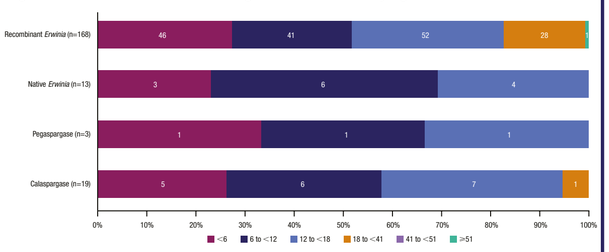
Table 2. ASP Treatment (Cohort A)

	E. coli ASP (n=1398)	*Erwinia* ASP (n=97)
Number of administrations		
Mean (SD)	2.7 (2.1)	14.4 (19.7)
Time from diagnosis to ASP use (days)		
Mean (SD)	95.0 (68.4)	125.7 (101.6)
Duration of treatment (days)		
Mean (SD)	66.5 (85.8)	63.5 (71.4)
Patients who switch, discontinue, or rechallenge after a delay in treatment, n (%)		
Patients with a delay	254 (18.2)	26 (26.8)
Patients who switch after a delay	23 (1.6)	2 (2.1)
Patients who discontinue after a delay	231 (16.5)	24 (24.7)
Patients who rechallenge after a delay	128 (9.2)	7 (7.2)
Treatment switches		
Frequency, n (%)	196 (14.0)	7 (7.2)
NSAA testing pattern		
Frequency, n (%)	423 (30.3)	12 (12.4)
Mean number of tests (SD)	1.4 (0.9)	1.6 (0.9)

ASP, asparaginase; *E. coli, Escherichia coli;* NSAA, nadir serum asparaginase activity; SD, standard deviation.

- Duration of treatment was similar between both groups; however those treated with *Erwinia* ASPs started treatment later and received more doses than those treated with *E. coli* ASPs
- Nadir serum ASP activity tests were more commonly performed in the group treated with *E. coli* ASPs compared to those treated with *Erwinia* ASPs (**Table 2**)

Figure 4. Distribution of Patients Using Each Formulation by Age in Cohort B



Second-Use ASP (Cohort B)

- Cohort B mostly consisted of patients (n=160, 78.8%) who switched or transitioned from pegaspargase to recombinant *Erwinia* ASP (**Figure 2**)
  - Within this subgroup, a 1:6 dose replacement ratio was observed within 21 days of the switch, with administrations most common on Mondays, Wednesdays, and Fridays
  - Of patients who switched to recombinant *Erwinia* ASP (from any ASP), most were <18 years old (n=139, 82.7% [**Figure 4**])
- Similar to Cohort A, most patients (n=112, 55.2%) presented without comorbidities (**Table 1**)
  - The top 3 comorbidities at baseline among patients in Cohort B were obesity (13.3%), liver disease (11.8%), and chronic obstructive pulmonary disease (10.3%)

Conclusions

- Consistent with the FDA approval, the first ASP that patients received was predominantly pegaspargase. However, native and recombinant *Erwinia* ASP were observed as the initial treatment of choice in 0.8% and 5.7% of patients, respectively, mostly aged <18 years old
- Most patients who switched ASP transitioned from pegaspargase to recombinant *Erwinia* were <18 years old
- Limitations of this study included
  - The nature of the database used
  - Data consisting mostly of outpatient hospital-based claims
  - The relatively short study timeframe resulting in limited sample size
- Future studies with a larger sample and additional data are needed to fully understand the real-world ASP use patterns and HSR rates in these patient populations

References: 1. Hijiya N et al. *Leuk Lymphoma.* 2016;57:748-757. **2.** Burke MJ. *Future Oncol.* 2014;10:2615-2627. **3.** van der Sluis IM et al. *Haematologica.* 2016;101:279-285. **4.** Gupta S et al. *J Clin Oncol.* 2020;38:1897-1905. **5.** Burke PW et al. *ESMO Open.* 2020;5:e000858. **6.** National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Acute Lymphoblastic Leukemia. Version 3.2023. 2023. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1410. **7.** RYLAZE® (asparaginase *erwinia* chrysanthemi (recombinant)-rywn) [package insert]. Jazz Pharmaceuticals, Inc. Palo Alto, CA. 2022. **8.** Maese L et al. *Front Pediatr.* 2022;10:902117.

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