Real-World Comparison of Healthcare Resource Utilization and Costs Between Patients With Chronic Lymphocytic Leukemia Treated With First-Line Ibrutinib or Acalabrutinib

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INTRODUCTION

- Ibrutinib (once-daily) and acalabrutinib (twice-daily) are Bruton's tyrosine kinase inhibitors (BTKis) recommended as first-line (1L) treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
- In several phase 3 clinical trials in 1L CLL/SLL, ibrutinib has demonstrated improved progression-free survival and overall survival relative to chemotherapy and/or chemoimmunotherapy and most recently, comparable overall survival to an age-matched general population in a pooled analysis;[1-5] the benefits of 1L ibrutinib have also been confirmed in a real-world setting across several studies[6]
- Real-world evidence comparing ibrutinib and acalabrutinib is starting to emerge, with 1L ibrutinib showing higher adherence and longer time to next treatment compared with 1L acalabrutinib in a population of patients treated in academic and non-teaching hospital systems in the United States[7-9]
- However, studies comparing healthcare resource utilization (HRU) and costs for patients with CLL/SLL treated with 1L single-agent ibrutinib or acalabrutinib remain scarce, with only 1 study performing early adherence and persistence using administrative claims data;[10] thus, results should be compared across a patient population treated in academic and non-teaching hospital systems in the United States who reached similar outcomes

OBJECTIVE

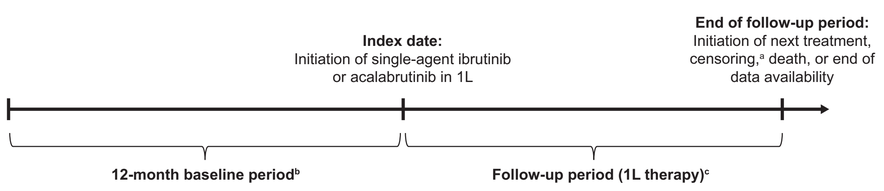
- To compare HRU and costs between patients with CLL/SLL treated with 1L ibrutinib or 1L acalabrutinib in real-world clinical practice

METHODS

Data Source

- This study used electronic medical records from the Acentrus database to identify patients treated with 1L ibrutinib or acalabrutinib between November 21, 2018, and April 30, 2022 in the United States
- Acentrus is a health system solution used by 128,000 prescribers/physicians, containing inpatient and outpatient data from 27 sites, including 10 National Cancer Institute designated sites, and 6 National Comprehensive Cancer network members
  - Acentrus data draw from both medication orders and refills
- Data include patient records from 12 non-teaching and 15 academic hospital systems across 15 states, which contain information on demographic characteristics, insurance plans, medications, visits, dates of deaths, diagnoses, laboratory test results, and vitals

FIGURE 1. Study design



[a]Patients were censored on the date of switch or add-on if they had 1 of the following: a within-class BTKi switch (i.e., the next treatment is also a BTKi) or an anti-CD20 antibody (i.e., obinutuzumab or rituximab) or venetoclax add-on to the index BTKi within 180 days post-index. [b]The baseline period was defined as the 12-month period prior to the index date. [c]The follow-up period was defined as the period from the index date to the earliest of initiation of second line (2L) therapy, death, or end of data availability.

1L, first-line.

Table 1. Imputation of medical and pharmacy costs

	Medical costs					
	Mean CLL-related costs PPPM from Fradley et al. [A]	Distribution of mean all-cause medical costs from Huang et al. [B]	Attribution of medical costs based on the distribution from Huang et al. [C] = [A] * [B]	Mean HRU PPPM from Fradley et al. [D]	Cost per visit (2021 USD) [E] = [C] / [D]	Inflation-adjusted cost per visit (2022 USD) [F] = [E] * 1.04
Ibrutinib						
Total medical costs	$3137	-	$3137	-	-	-
Inpatient	-	21.3%	$668	0.04	$16,709	$17,386
ED	-	8.1%	$254	0.03	$8467	$8810
Outpatient	-	64.4%	$2022	1.44	$1404	$1461
Other services	-	6.1%	$193	0.35	$551	$573
Acalabrutinib						
Total medical costs	$2656	-	$2656	-	-	-
Inpatient	-	21.3%	$566	0.03	$18,863	$19,627
ED	-	8.1%	$215	0.02	$10,753	$11,189
Outpatient	-	64.4%	$1712	1.47	$1164	$1212
Other services	-	6.1%	$163	0.29	$563	$586

	Pharmacy costs			
	Mean pharmacy costs PPPM from Fradley et al. [A]	Mean adherence at 6 months from Fradley et al. [B]	Pharmacy costs PPPM assuming 100% adherence (2021 USD) [C] = [A] / [B]	Inflation-adjusted pharmacy costs PPPM (2022 USD) [D] = [C] * 1.04
Ibrutinib	$12,315	0.86	$14,320	$14,900
Acalabrutinib	$12,513	0.85	$14,721	$15,318

CLL, chronic lymphocytic leukemia; ED, emergency department; HRU, healthcare resource utilization; PPPM, per-patient-per-month; USD, United States dollars.

Statistical analysis

- Comparisons between cohorts were made using multivariate Poisson regression models for HRU (ie, number of visits per month) and linear regression models for costs
- All models were adjusted for baseline demographic (age, sex, region, race, year of index date) and clinical characteristics (Quan-Charlson Comorbidity Index [Quan-CCI], chronic pulmonary disease, peripheral vascular disease, hypertension, AF, metastatic cancer, use of corticosteroids, and use of antiplatelets)
- To account for the overdispersion of HRU and cost outcomes, non-parametric bootstrap procedures with 500 replications were used to calculate 95% CIs and *P* values

RESULTS

Baseline Demographics and Clinical Characteristics

- A total of 710 and 373 patients initiated 1L single-agent ibrutinib and acalabrutinib, respectively (**Table 2**)
- Mean [median] duration of 1L was longer for ibrutinib compared with acalabrutinib (15.6 [16.5] vs 11.1 [10.2] months, *P* < 0.001)
- Mean age (ibrutinib vs acalabrutinib: 71.5 vs 72.4 years, *P* = 0.159), sex (38.5% vs 38.3%, *P* = 0.971), and mean Quan-CCI (3.1 vs 3.0, *P* = 0.597) were similar between the two cohorts (**Table 2**)

Comparison of HRU and costs

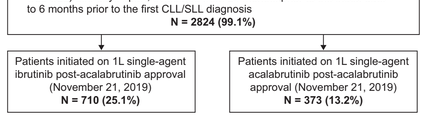
- During 1L therapy, the mean all-cause number of inpatient days was similar for both cohorts (ibrutinib vs acalabrutinib: 0.42 vs 0.49 days PPPM; rate ratio [RR] = 1.00; *P* = 0.966), while the mean number of all-cause outpatient visits was significantly lower for ibrutinib compared with acalabrutinib (1.47 vs 2.06 days PPPM; RR = 0.76; *P* < 0.001) (**Figure 3**).
  - The lower number of outpatient visits for ibrutinib vs acalabrutinib was driven by a lower number of visits for management of CLL/SLL and laboratory testing (e.g., complete blood count or metabolic panel)
- Similar results were observed for CLL/SLL-related HRU (outpatient: RR = 0.80; *P* = 0.036) and among the subgroup of patients with baseline AF (all-cause outpatient: RR = 0.53; *P* = 0.044) (**Figure 3**)

- Data are de-identified and comply with the patient requirements of the Health Insurance Portability and Accountability Act

Patients and study design

- In this retrospective cohort study, the index date was defined as the date of ibrutinib or acalabrutinib initiation as 1L treatment on or after November 21, 2019 (**Figure 1**)
  - A washout period of ≥ 12 months of data availability prior to the index date without any use of antineoplastic agents was used to identify 1L therapy
  - A window of 28 days post-index was used to ascertain that no other antineoplastic agents were used in combination with ibrutinib or acalabrutinib
- Patient selection criteria are presented in **Figure 2**

Figure 2. Study population selection



1L, first-line; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

- A subgroup of patients with atrial fibrillation (AF) during the baseline period was also analyzed

Outcomes

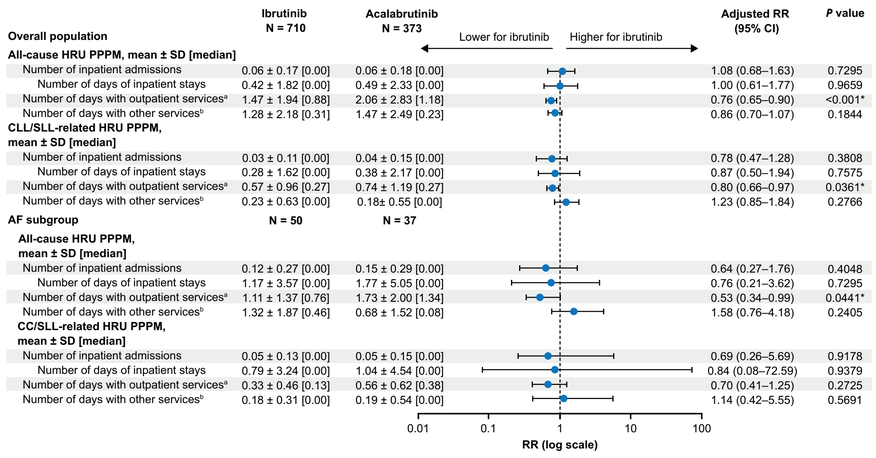
- Per-patient-per-month (PPPM) HRU and costs were evaluated during the entire duration of 1L therapy, and during the first 3, 6, and 12 months of 1L therapy
- HRU outcomes included inpatient admissions, outpatient visits (including outpatient hospital, office, emergency department [ED], and other outpatient services), and other services (services other than inpatient or outpatient)
- Cost outcomes included medical costs, pharmacy costs, and total costs (sum of medical and pharmacy costs)
  - Guided by prior literature,[11-14] cost information was imputed based on HRU results and available literature[10,15] where costs per visit could be calculated (**Table 1**)

Table 2. Baseline demographics and clinical characteristics

	Ibrutinib N = 710	Acalabrutinib N = 373	*P* value
Age at index date, mean ± SD [median]	71.5 ± 10.4 [73.0]	72.4 ± 9.8 [72.0]	0.159
Female, n (%)	273 (38.5)	143 (38.3)	0.971
Year of index date, n (%)			
2019	45 (6.3)	7 (1.9)	0.001*
2020	408 (57.5)	119 (31.9)	< 0.001*
2021	217 (30.6)	200 (53.6)	< 0.001*
2022	40 (5.6)	47 (12.6)	< 0.001*
US region, n (%)			
South	213 (30.0)	138 (37.0)	0.019*
West	212 (29.9)	118 (31.6)	0.546
Midwest	188 (26.5)	86 (23.1)	0.218
Northeast	21 (3.0)	9 (2.4)	0.604
Unknown	76 (10.7)	22 (5.9)	0.009*
Race, n (%)			
White	320 (45.1)	150 (40.2)	0.125
Black	25 (3.5)	19 (5.1)	0.213
Asian	13 (1.8)	7 (1.9)	0.958
Other	352 (49.6)	197 (52.8)	0.311
Quan-CCI, mean ± SD [median]	3.1 ± 1.7 [2.0]	3.0 ± 1.7 [2.0]	0.597
Comorbidities, n (%)			
Chronic pulmonary disease	94 (13.2)	32 (8.6)	0.023*
Peripheral vascular disease	54 (7.6)	15 (4.0)	0.022*
Hypertension	294 (41.4)	120 (32.2)	0.003*
AF	50 (7.0)	37 (9.9)	0.098
Metastatic cancer	17 (2.4)	17 (4.6)	0.052
Medication use, n (%)			
Corticosteroids	103 (14.5)	75 (20.1)	0.018*
Antiplatelets	50 (7.0)	13 (3.5)	0.017*

**P* value ≤ 0.05.
AF, atrial fibrillation; Quan-CCI, Quan-Charlson Comorbidity Index; SD, standard deviation; US, United States.

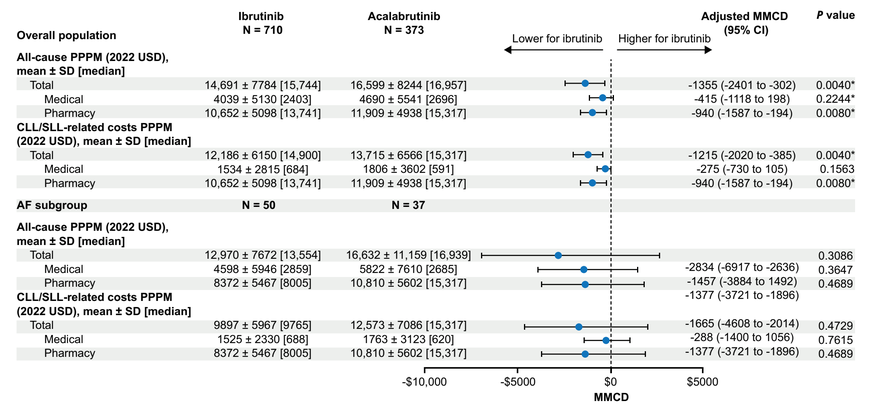
Figure 3. Comparison of HRU in patients with CLL/SLL initiating 1L ibrutinib or acalabrutinib



**P* value ≤ 0.05.
[a]Outpatient services included outpatient hospital, office, other outpatient services, and emergency department visits. [b]Other services included all services not identified in Acentrus ("no information", "other", "unknown", "unspecified"), or where the place of service was listed as "home".
1L, first-line; AF, atrial fibrillation; CI, confidence interval; CLL, chronic lymphocytic leukemia; HRU, healthcare resource use; PPPM, per-patient-per-month; RR, rate ratio; SD, standard deviation; SLL, small lymphocytic lymphoma.

- Mean all-cause and CLL/SLL-related total healthcare costs were significantly lower for ibrutinib compared with acalabrutinib (all-cause: $14,691 vs $16,599 PPPM; mean monthly cost difference [MMCD] = -$1355; *P* = 0.004; CLL/SLL-related: $12,186 vs $13,715 PPPM; MMCD = -$1215; *P* = 0.004) (**Figure 4**)
- Similar results were observed for the subgroup of patients with baseline AF (all-cause MMCD = -$2834; *P* = 0.309) (**Figure 4**)

Figure 4. Comparison of costs in patients with CLL/SLL initiating 1L ibrutinib or acalabrutinib



**P* value ≤ 0.05.
1L, first-line; AF, atrial fibrillation; CI, confidence interval; CLL, chronic lymphocytic leukemia; MMCD, mean monthly cost difference; PPPM, per-patient-per-month; SD, standard deviation; SLL, small lymphocytic lymphoma; USD, United States dollars.

- HRU and cost results were also consistent for the first 3, 6, and 12 months of 1L therapy (**Table 3**)

Table 3. HRU and costs during the first 3, 6, and 12 months of 1L therapy

	Ibrutinib N = 710	Acalabrutinib N = 373	Adjusted RR or MMCD (95% CI)	*P* value
First 3 months of 1L therapy				
All-cause HRU PPPM, mean ± SD [median]				
Number of inpatient admissions	0.07 ± 0.25 [0.00]	0.07 ± 0.20 [0.00]	1.06 (0.67 to 1.58)	0.8457
Number of days of inpatient stays	0.49 ± 2.08 [0.00]	0.51 ± 2.33 [0.00]	1.11 (0.67 to 1.95)	0.6814
Number of days with outpatient services[a]	1.97 ± 2.21 [1.32]	2.62 ± 3.13 [1.65]	0.76 (0.66 to 0.88)	< 0.001*
Total costs PPPM (2022 USD), mean ± SD [median]				
All-cause	18,768 ± 7497 [17,789]	19,704 ± 7419 [18,513]	-810 (-1886 to 121)	0.1202
CLL/SLL-related	15,578 ± 5175 [15,845]	16,248 ± 5546 [16,090]	-788 (-1502 to -38)	0.0401*
First 6 months of 1L therapy				
All-cause HRU PPPM, mean ± SD [median]				
Number of inpatient admissions	0.06 ± 0.19 [0.00]	0.06 ± 0.20 [0.00]	1.00 (0.65 to 1.49)	0.9579
Number of days of inpatient stays	0.46 ± 1.90 [0.00]	0.52 ± 2.37 [0.00]	1.03 (0.64 to 1.80)	0.8497
Number of days with outpatient services[a]	1.76 ± 2.03 [1.29]	2.32 ± 2.83 [1.49]	0.77 (0.66 to 0.89)	< 0.001*
Total costs PPPM (2022 USD), mean ± SD [median]				
All-cause	17,238 ± 7077 [17,174]	18,431 ± 7603 [17,798]	-1040 (-2096 to -118)	0.0441*
CLL/SLL-related	14,372 ± 5426 [15,384]	15,144 ± 5849 [15,706]	-807 (-1563 to -117)	0.0281*
First 12 months of 1L therapy				
All-cause HRU PPPM mean ± SD [median]				
Number of inpatient admissions	0.06 ± 0.17 [0.00]	0.06 ± 0.18 [0.00]	1.03 (0.68 to 1.53)	0.9138
Number of days of inpatient stays	0.43 ± 1.83 [0.00]	0.51 ± 2.35 [0.00]	0.98 (0.61 to 1.71)	0.9379
Number of days with outpatient services[a]	1.59 ± 1.97 [1.02]	2.14 ± 2.80 [1.33]	0.76 (0.65 to 0.89)	< 0.001*
Total costs PPPM (2022 USD), mean ± SD [median]				
All-cause	15,804 ± 7431 [16,443]	17,341 ± 7898 [17,331]	-1417 (-2448 to -470)	< 0.001*
CLL/SLL-related	13,173 ± 5882 [15,021]	14,328 ± 6271 [15,477]	-1218 (-2025 to -426)	< 0.001*

**P* value ≤ 0.05.
[a]Outpatient services included outpatient hospital, office, other outpatient services, and emergency department visits.
CLL, chronic lymphocytic leukemia; CI, confidence interval; HRU, healthcare resource utilization; MMCD, mean monthly cost difference; PPPM, per-patient-per-month; RR, rate ratio; SD, standard deviation; SLL, small lymphocytic lymphoma; USD, United States dollars.

LIMITATIONS

- While results of this study may not be generalizable to all patients with CLL/SLL treated with 1L ibrutinib or acalabrutinib, this real-world study is one of the largest studies reflecting the experience of patients treated in academic and non-teaching hospital systems, as it covered many sites across the United States and had a small list of eligibility criteria relative to clinical trials; furthermore, it leveraged a data source that was rich in demographic and clinical information
- As with any studies imputing costs,[11-14] the estimated costs calculated in the current study assumed the same mean cost for all units of a given HRU; therefore, the intensity of a unit of HRU (e.g., 1 outpatient visit) did not vary between patients
- Cost information was imputed based on insurance claims data from the Acentrus database, and may not be representative of other insurance plans or patients studied in other databases

CONCLUSIONS

This real-world comparative analysis showed that patients with CLL/SLL treated with 1L ibrutinib had a lower number of days with outpatient services and lower all-cause and CLL/SLL-related costs compared with acalabrutinib, potentially indicating the need for greater monitoring among patients treated with acalabrutinib

Results were consistent among the subgroup of patients with baseline AF and during the first 3, 6, and 12 months of 1L therapy

These real-world findings, in combination with previous studies showing higher adherence[8, 9] and longer time to next treatment[7] for 1L ibrutinib, support the use of ibrutinib as an optimal BTKi in 1L therapy

Additional research is warranted to understand the reasons behind differences in HRU and costs between 1L ibrutinib and acalabrutinib

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References

1. Burger JA, et al. *N Engl J Med*. 2015;373(25):2425-37;
2. Moreno C, et al. *Lancet Oncol*. 2019;20(1):43-56;
3. Shanafelt TD, et al. *N Engl J Med*. 2019;381(5):432-443;
4. Woyach JA, et al. *N Engl J Med*. 2018;379(26):2517-2528;
5. Ghia P, et al. *Blood*. 2022;140:4159-4161;
6. Lee P, et al. *Drugs Real World Outcomes*. 2023;10(1):11-22;
7. Jacobs R, et al. *Future Oncol*. 2023;10.2217/fon-2023-0436;
8. Lu X, et al. *Clin Lymphoma Myeloma Leuk*. 2022;22:S280-S281;
9. Lu X, et al. *Patient Prefer Adherence*. 2023;17:2073-2084;
10. Fradley M, et al. *Blood*. 2022;140:10983–10984;
11. Morrison L, et al. *J Manag Care Spec Pharm*. 2023;29(2):161-171;
12. Maeng DD, et al. *Pain Res Manag*. 2015;20(5):234-40;
13. Sheffield BS, et al. *Curr Oncol*. 2023;30(2):2348-2365;
14. Korjian S, et al. *Am J Cardiol*. 2019;123(3):355-360;
15. Huang Q, et al. *Curr Med Res Opin*. 2020;36(12):2009-2018.

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