Treatment Patterns Among Medicare Advantage CLL/SLL Patients During First 12 Months After Ibrutinib Start: Real World Claims Analysis

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Bruton tyrosine kinase (BTK) inhibitors have greatly improved outcomes for chronic lymphocytic leukemia (CLL), the most common leukemia in adults [1] and small cell lymphocytic lymphoma (SLL) but known adverse events (AEs) associated with BTK inhibitors present challenges. Ibrutinib, the first BTK inhibitor to market for treatment of CLL/SLL in 2014, is associated with AEs which can lead to discontinuation and/or down dosing. [2] [3] [4] [5] [6] [7] In one study, 41% of patients discontinued ibrutinib (median time to discontinuation was 7 months), with ibrutinib toxicity listed as the most common reason for discontinuation. [7] Atrial fibrillation (AF) development is a known AE associated with BTK inhibitor treatment consistently reported in clinical trials. In a meta-analysis of 8 randomly controlled trials, ibrutinib was associated with a 4-fold increase in the risk of AF. [8] Interim results from the global phase III ALPINE trial reported significantly higher rates of AF development for patients treated with first generation ibrutinib versus second generation zanubrutinib. [9]

We analyzed CLL/SLL patients newly starting ibrutinib in our Medicare Advantage with Part D (MAPD) claims data to evaluate rates of ibrutinib discontinuation and down dosing, new AE development, and in particular, the incidence of new AF development. At the time of this analysis, we had data through 2019 and excluded acalabrutinib users because FDA approval did not occur until November 2019.

Methodology and Data Source

Data Source
We used 2015-2019 Milliman proprietary MAPD claims data. The database contains annual enrollment and all Parts A, B, and D claims for approximately 2.5 million annual members. Member identification codes are consistent from year to year and allow for multiyear longitudinal studies.

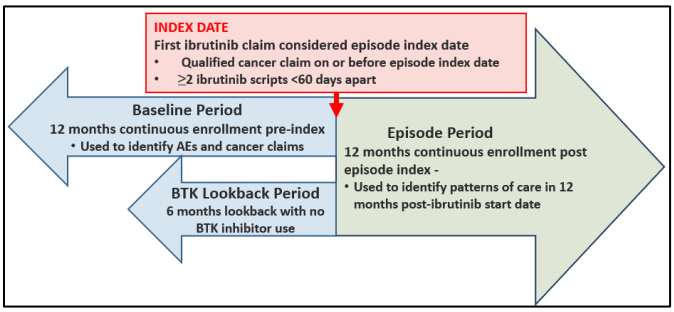
Three index years (2016-2018) were used to identify CLL/SLL members newly starting ibrutinib, with 2015 used as a "look back" year for 2016 index cases and 2019 used as a "look forward" year for 2018 index cases.

Study Population Identification
The denominator population was required to be ≥18 and have at least one month of MAPD enrollment with both medical and pharmacy coverage in 2016-2019. CLL/SLL patients were identified as those with at least two qualified claims on different dates of service (minimum 7 days and maximum of 6 months apart) coded with a diagnosis for CLL/SLL in any position on the claim. Ibrutinib use was identified based on NDC codes.

To qualify for the 12-month post-ibrutinib episode analysis, a CLL/SLL ibrutinib patient was required to have:

- At least two sequential prescription fills of ibrutinib with a gap of less than 60 day's supply between fills and no fills for a different BTK inhibitor product in that time period
- A 6-month look back period without BTK inhibitor use (first ibrutinib claim considered episode index date)
- 12 months of continuous enrollment prior to and after the episode index date
- A qualified CLL/SLL claim on or before the episode index date

Figure 1: Episode Definition



Outcome Metric Identification
Discontinuing patients were defined as patients who did not receive any ibrutinib script for at least 2 months (60 days) during the episode period. Down dosing patients were defined as patients who received an additional ibrutinib script for a lower average mg/day (total quantity dispensed/days' supply), per prescribing information. Adverse Events (AEs) were defined as medical conditions or events that were potentially related to ibrutinib use. "New" AEs were medical conditions/events coded in the 12 months following the first ibrutinib script, but not coded in the baseline period. AF patients were identified if they had 1 or more qualified claims coded with a diagnosis for atrial fibrillation/flutter in any position on the claim.

Healthcare costs reflect the allowed amount paid by the MAPD plan plus patient cost sharing for all Part A and B covered services. Prescription drug Part D costs reflect total reimbursement including coverage gap and catastrophic coverage amounts and do not represent the amount the MAPD plan is liable for. All costs have been trended to 2019 using the

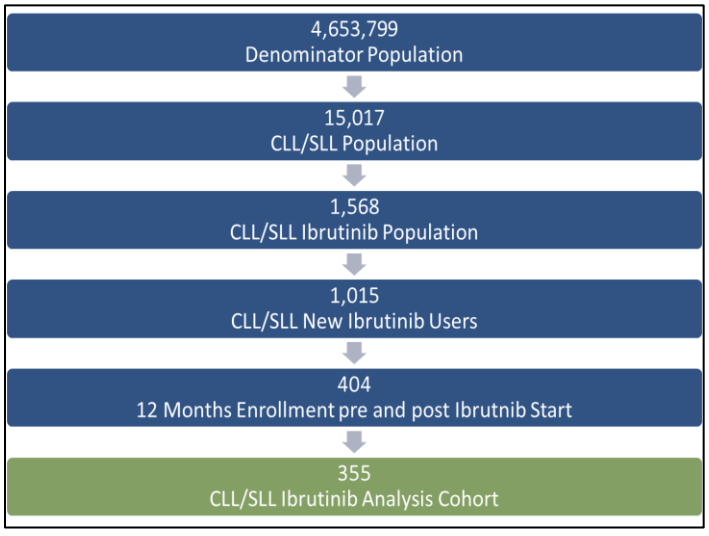
Milliman Health Cost Guideline (HCG) trend factors. The average cost contributed by each healthcare service reflects the total costs incurred by that service during the episode period divided by the patients in the study cohort and does not reflect the average cost of the service for an individual who incurred the service.

Detailed code sets for identification of the study population and all AEs available upon request.

Results

355 CLL/SLL patients newly starting ibrutinib were identified who met the episode analysis eligibility criteria (Figure 2). The denominator population (N=4,653,799) included beneficiaries ≥18 with at least one month of medical and pharmacy coverage in 2016-2019. The CLL/SLL population (N=15,017) consisted of patients with two qualified claims for CLL/SLL occurring within 7 days and 6 months of one another during 2016-2019. The CLL/SLL ibrutinib population (N=1,568) had two scripts for ibrutinib in any of the years 2016-2019. CLL/SLL new ibrutinib users (N=1,015) had no BTK use observed in a 6-month period prior to the first observed ibrutinib script (index date) and they had a qualified claim for CLL/SLL on or before the index date. CLL/SLL new ibrutinib users who had 12 months of continuous enrollment pre and post ibrutinib start (N=404) were then identified; this removed patients with 2019 index dates. The final analysis cohort group (N=355) required that the second ibrutinib claim occurred within 60 days following the index ibrutinib claim (index date).

Figure 2: Study Population Flow Chart

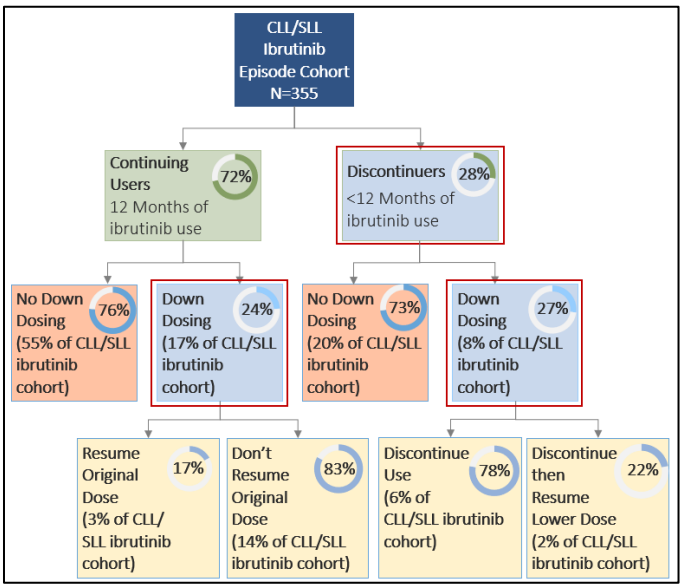


Source: 2015-2019 Milliman proprietary MAPD Data

Demographics and Treatment Patterns

The average age of the ibrutinib CLL/SLL episode cohort was 76.3 years and 61% were male. Of these patients, 28% discontinued ibrutinib within 12 months, with an average of 3.8 months to discontinuation, and 25% down dosed from their original dose of ibrutinib, with an average of 4.4 months to down dosing. See Figure 3.

Figure 3: CLL/SLL Ibrutinib Cohort Treatment Patterns



Source: 2015-2019 Milliman proprietary MAPD Data
Discontinuation: No ibrutinib script for ≥60 days during the episode period
Down Dosing: Received an additional ibrutinib script for lower average mg/day

Adverse Events

Atrial Fibrillation was the most frequent new AE condition appearing in the 12 months after ibrutinib start. See Figure 4.

Figure 4: AE Rates 12 Months Before and After Ibrutinib Start

Adverse Events Before and During 12 Month Episode				
Adverse Events	**% Patients Coded with AEs During Baseline Period**	**% Patients with New AE (Episode Only)**	**% of AE Group Who DD Within 2 Months of First New AE**	**% of AE Group Who DC Within 2 Months of First New AE**
Total Patients		**355**		
% of Patients with 1+ New AE		**78.9%**	**12.5%**	**18.2%**
Conditions Possibly Related to Ibrutinib Use				
Atrial Fibrillation/Flutter	12.4%	13.5%	8.9%	36.4%
Gastroesophageal Reflux Disease	31.0%	13.2%	2.3%	23.3%
Heart Failure	11.8%	12.7%	6.8%	25.0%
Hypertension	69.6%	9.6%	9.7%	12.9%
Ventricular Arrhythmia	11.0%	7.0%	9.1%	27.3%
Peripheral Neuropathy	10.1%	6.2%	0.0%	5.9%
Chronic Kidney Disease	15.2%	5.9%	4.8%	23.8%
Type 2 Diabetes (T2DM)	24.8%	4.5%	0.0%	18.8%
Peptic Ulcer Disease	1.7%	3.4%	0.0%	12.5%
Myocardial infarction	0.6%	1.1%	25.0%	0.0%
Stroke	0.0%	0.8%	0.0%	33.3%
Severe Liver Disease	3.1%	0.6%	0.0%	0.0%
End-Stage Renal Disease (ESRD)	0.6%	0.6%	0.0%	0.0%
Events Possibly Related to Blood Cancer or Ibrutinib Use				
Arthralgia/Myalgia	24.8%	21.1%	9.2%	6.2%
Anemia (mild to severe)	45.1%	15.2%	10.4%	8.5%
Edema	14.9%	14.6%	4.5%	15.9%
Other Infection (severe, all-cause)	12.4%	14.1%	6.8%	29.5%
Fatigue	27.0%	13.0%	2.6%	15.8%
Petechiae/Purpura/Rash	14.6%	12.4%	20.5%	11.1%
Acute Kidney Injury (severe, all-cause)	7.3%	9.6%	12.5%	32.3%
Thrombocytopenia	27.0%	9.0%	12.9%	22.6%
Abdominal Pain	12.7%	9.0%	11.5%	7.7%
Diarrhea	9.3%	8.7%	14.3%	10.7%
Fever	6.5%	6.8%	8.7%	30.4%
Headache	5.6%	6.8%	4.5%	22.7%
Major Bleeding (severe, all-types)	2.5%	5.1%	12.5%	25.0%
Sepsis (all-cause)	4.8%	5.1%	0.0%	38.5%
Neutropenia	5.9%	3.4%	0.0%	33.3%
Muscle spasm	0.8%	1.7%	0.0%	0.0%
Mouth ulcer	0.3%	1.4%	40.0%	20.0%

Source: 2015-2019 Milliman proprietary MAPD Data

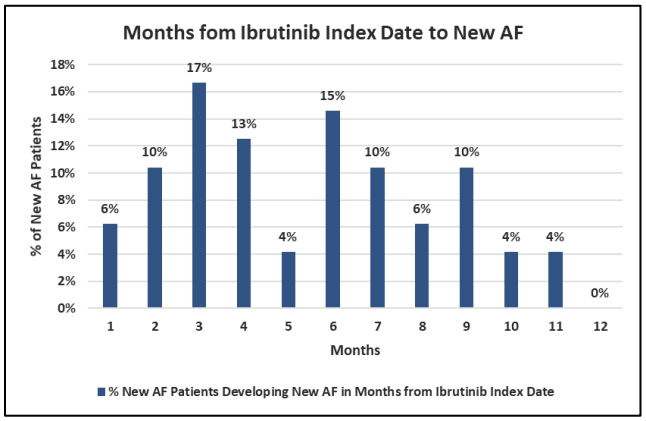
The incidence rate of new AF in the baseline 12 months prior to ibrutinib start was 2.2%. This rate was based on 185 CLL/SLL ibrutinib patients having eligibility for at least 12 months prior to the baseline period (24 months prior to ibrutinib start), and 4 of those patients having AF coded in the baseline but not between 12 and 24 months prior to ibrutinib start. The incidence rate of new AF in the 12 months following ibrutinib start was 13.5% (48 patients with new AF out of 355 total patients). The difference in incidence rates between the year before and after ibrutinib start was statistically significant (p-value<0.0001).

Costs, Outcomes, and Treatment Patterns among patients with Atrial Fibrillation

We compared key metrics for those with new AF in the 12 months after ibrutinib start (N=48) to those without new AF (N=307). The average age of the new AF cohort was 77.4 years and 60% were male; those without new AF had an average age of 76.1 years and 61% were male.

The average number of months to new AF development was 5.4, but new AF development continued to occur over the first 11 months. See Figure 5.

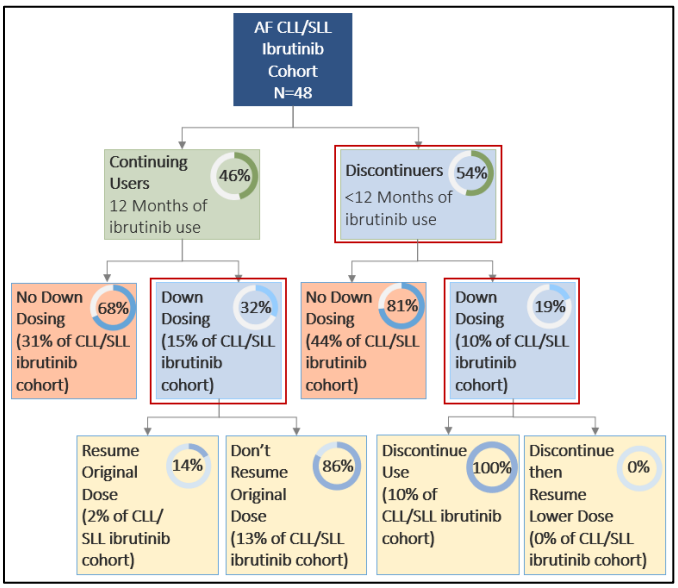
Figure 5: Months from Ibrutinib Index Date to New AF



Source: 2015-2019 Milliman proprietary MAPD Data

New AF patients had a statistically significantly higher rate of ibrutinib discontinuation in the 12 months after ibrutinib start compared to those without new AF: 54% vs 24% respectively (p-value=0.0002). The majority of the new AF patients that discontinued did so after the first AF occurrence (73%), with 36% discontinuing within 2 months. 25% of new AF patients down dosed, which was a similar rate to those without AF (24%); 42% of new AF patients who down dosed did so after the first AF occurrence. See Figure 6.

Figure 6: New AF CLL/SLL Ibrutinib Cohort Treatment Patterns



Source: 2015-2019 Milliman proprietary MAPD Data
Discontinuation: No ibrutinib script for ≥60 days during the episode period
Down Dosing: Received an additional ibrutinib script for lower average mg/day

50% of new AF patients had at least one inpatient (IP) admission within 30 days of their first AF occurrence; 42% of those admissions were for cardiac arrhythmias. See Figure 7.

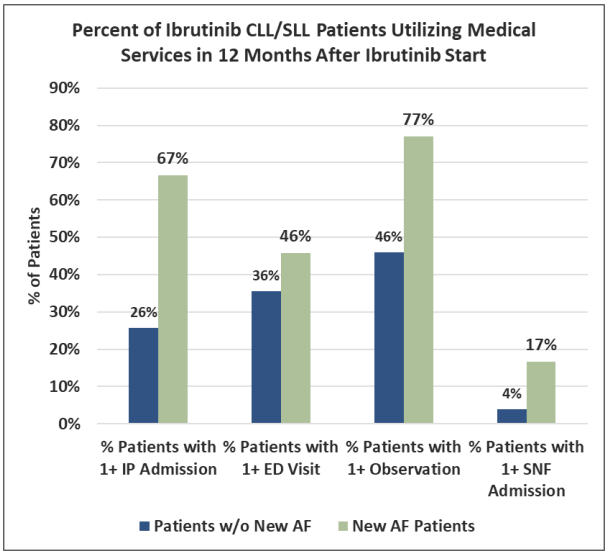
Figure 7: Inpatient Admissions for New AF Patients

% of New AF Patients with 1+ IP Admission within 30 Days from First AF Occurrence	50%
Total Admissions	**26**
Cardiac Arrhythmias	42%
Respiratory Infection	12%
Respiratory Failure	8%
Heart Failure	8%
Head and Neck Disease	4%
Respiratory Disease	4%
Pneumonia	4%
Cardiothoracic Procedures	4%
Circulatory Diseases - Medical	4%
Sepsis	4%
Cerebrovascular Disease - Medical	4%
Gastrointestinal Disease - Medical	4%

Source: 2015-2019 Milliman proprietary MAPD Data

We compared healthcare resource utilization and costs in the 12 months after ibrutinib start between those with and without new AF. Patients with new AF were 2.6 times more likely to have an inpatient stay, 1.3 times more likely to have an emergency department (ED) visit, 1.7 times more likely to have an observation stay, and 4.3 times more likely to have a SNF admission compared to those without new AF. All were statistically significantly higher for the new AF population (p-value<0.05). See Figure 8.

Figure 8: Utilization Patterns in the 12 Months after Ibrutinib Start for New AF Patients vs Patients Without New AF



Source: 2015-2019 Milliman proprietary MAPD Data

Non-ibrutinib average annual allowed costs were statistically significantly higher for new AF patients during the 12 months after ibrutinib start compared to non-AF patients (p-value<0.0001). This was driven by higher costs across all services, including inpatient hospital stays, post-discharge care, professional claims, ED visits, non-ibrutinib chemo claims, and non-chemo Part D drugs. See Figure 9.

Figure 9: Average Annual Cost for New AF vs non-AF Patients

Metrics	Patients w/o New AF	% Contribution to Total Spend	New AF Patients	% Contribution to Total Spend
Number of Patients	**307**		**48**	
Average Months on Ibrutinib	**10.6**		**8.8**	
Total Cost of Care	**$156,871**	**100.0%**	**$153,710**	**100.0%**
Ibrutinib Part D	**$129,296**	**82.4%**	**$105,460**	**68.6%**
Total Non-Ibrutinib Costs:	**$27,574**	**17.6%**	**$48,250**	**31.4%**
Inpatient Hospital	$4,458	16.2%	$12,604	26.1%
Outpatient Hospital	$10,832	39.3%	$12,807	26.5%
ED/Obervation	$785	2.8%	$1,452	3.0%
Professional	$7,206	26.1%	$11,058	22.9%
SNF/Home Health/Hospice	$923	3.3%	$2,763	5.7%
Chemotherapy Administration	$203	0.7%	$503	1.0%
Part B Chemo	$3,484	12.6%	$5,976	12.4%
Other Part B Drugs	$4,112	14.9%	$4,311	8.9%
Part D Chemo	$537	1.9%	$1,774	3.7%
Other Part D Drugs	$3,153	11.4%	$6,330	13.1%

Source: 2015-2019 Milliman proprietary MAPD Data
Reflects allowed costs (plan paid amounts + patient cost sharing); Part D costs are total reimbursement including coverage gap and catastrophic coverage period amounts and do not represent the amount the MAPD plan is liable for; Costs have been trended to 2019 using the Milliman HCGs; BTK inhibitors are reflected in "Ibrutinib Part D" service line, not "Part D Chemo"

New AF patients who discontinued ibrutinib had statistically significantly higher non-ibrutinib costs compared to new AF patients that didn't discontinue ibrutinib (p-value=0.019). See Figure 10.

Figure 10: Average Annual Cost for New AF Patients Discontinuing Ibrutinib vs New AF Patients Continuing Ibrutinib

Metrics	Continuing Users	% Contribution to Total Spend	Discontinuers	% Contribution to Total Spend
Number of Patients	**22**		**26**	
Average Months on Ibrutinib	**12.0**		**6.1**	
Total Cost of Care	**$196,153**	**100.0%**	**$117,796**	**100.0%**
Ibrutinib Part D	**$160,921**	**82.0%**	**$58,531**	**49.7%**
Total Non-Ibrutinib Costs:	**$35,232**	**18.0%**	**$59,265**	**50.3%**
Inpatient Hospital	$9,348	26.5%	$15,359	25.9%
Outpatient Hospital	$7,493	21.3%	$17,303	29.2%
ED/Obervation	$956	2.7%	$1,871	3.2%
Professional	$10,738	30.5%	$11,329	19.1%
SNF/Home Health/Hospice	$1,439	4.1%	$3,884	6.6%
Chemotherapy Administration	$64	0.2%	$874	1.5%
Part B Chemo	$1,679	4.8%	$9,612	16.2%
Other Part B Drugs	$3,852	10.9%	$4,700	7.9%
Part D Chemo	$0	0.0%	$3,276	5.5%
Other Part D Drugs	$5,366	15.2%	$7,145	12.1%

Source: 2015-2019 Milliman proprietary MAPD Data
Reflects allowed costs (plan paid amounts + patient cost sharing); Part D costs are total reimbursement including coverage gap and catastrophic coverage period amounts and do not represent the amount the MAPD plan is liable for; Costs have been trended to 2019 using the Milliman HCGs; BTK inhibitors are reflected in "Ibrutinib Part D" service line, not "Part D Chemo"

Conclusions

This claims-based analysis indicates that CLL/SLL patients taking ibrutinib had an increased rate of AF development in the 12 months following ibrutinib start. For those who develop AF, there was a higher rate of ibrutinib discontinuation in the 12 months following ibrutinib start compared to those without new AF, and 73% of those that discontinued did so within 2 months after the first AF occurrence. New AF patients had a higher rate of healthcare utilization and non-ibrutinib costs in the 12 months after ibrutinib start compared to those without new AF, highlighting the burden associated with AF development in new ibrutinib users. Alternative BTK inhibitor therapies are emerging to address the high rate of AEs in CLL/SLL patients.

Caveats and Limitations

This report was commissioned by BeiGene, who manufactures the BTK inhibitor zanubrutinib. The findings and conclusions reflect the opinion of the authors; Milliman does not endorse any policy or product. If this report is reproduced, we ask that it be reproduced in its entirety, as pieces taken out of context can be misleading. The results presented here are based on Milliman's analysis of the 2016-2019 Milliman proprietary MAPD data. Different data sets, time periods, and methodologies may produce different results. Claims based analyses reflect provider coding which may not capture all healthcare utilization. New AE identification is based on no coding of the AE during the 12 month baseline period prior to ibrutinib start and does not capture AE coding prior to the baseline period. Code sets for identification criteria are available upon request.

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