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Real-World Evidence Associated With a First-Generation BTK Inhibitor in Patients With CLL/SLL

This Product Theater Recap from *The American Journal of Managed Care*® (AJMC®) provides key information regarding a Science & Innovation Theater presented by Kathryn Fitch, MD, RN, principal and health care consultant from Milliman, Inc., at the Academy of Managed Care Pharmacy (AMCP) Nexus 2021 on Wednesday, October 20, 2021. The presentation was sponsored by BeiGene, USA. Insights from Ms Fitch and Michael Kolodziej, MD, FACP, senior advisor at ADVI Health, LLC, on this presentation and the potential implications of its results for managed care are included in a Q&A that appears at the end of this publication.

Patients who developed atrial fibrillation (AF) within the first 12 months of starting treatment with a first-generation Bruton tyrosine kinase (BTK) inhibitor for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) discontinued therapy at a greater rate, utilized health care resources at a greater rate, and incurred higher average nontreatment-related health care costs during that period than did patients who did not develop AF, according to the results of a claims-based analysis presented at AMCP Nexus 2021, held from October 18 to 21, 2021, in Denver, Colorado.¹

BACKGROUND

Adults experience CLL at a greater rate than they do any type of other leukemia.² In 2014, ibrutinib became the first BTK inhibitor approved by the FDA for the treatment of CLL.^{3,4} In a 3-year safety study of patients with CLL/SLL taking a daily dose of this first-generation medication (n=132), ibrutinib was shown to have both a high response rate that increased in quality and frequency over time and modest toxicity.⁵ Evidence also has shown that treatment with ibrutinib is associated with adverse events (AEs) that can lead to discontinuation and/or down-dosing.⁶

Patients with CLL have been shown to discontinue treatment with ibrutinib therapy. In a multi-center, retrospective analysis of patients with CLL who had been treated with ibrutinib (N=616), 41% of patients discontinued the treatment (median time to discontinuation, 7 months [range, 0.1-41 months]). Ibrutinib toxicity was listed as the most common reason for discontinuation by 63.1% of patients discontinuing ibrutinib in the frontline setting (12 of 80 patients) and 50.2% of patients discontinuing the treatment in the relapsed/refractory setting (116 of 536 patients).⁷

AF is a known AE associated with BTK inhibitor treatment that is consistently reported in clinical trials.⁸ The results of a 2017 analysis of pooled data from 4 large, randomized controlled trials (RCTs) found that patients treated with ibrutinib had a higher estimated cumulative incidence of AF than did those treated with a comparator agent (7.4% [95% CI, 5.6%-9.6%] vs 1.9% [95% CI, 1.0%-3.4%]). Of the 1505 patients included in the analysis, 139 patients had previously treated mantle cell lymphoma (MCL), and 1366 patients had newly diagnosed or previously treated CLL.⁸ Moreover, the results of a 2019 systematic review with a meta-analysis of 8 RCTs (6 RCTs in patients with CLL, 1 RCT in patients with MCL, and 1 RCT in patients with Waldenström macroglobulinemia) that compared patients treated with ibrutinib with any control group (ie, using placebo, no treatment, or any active drug)

showed that the use of ibrutinib was associated with a more than 4-fold increase in the risk of AF (pooled risk ratio, 4.69; 95% CI, 2.17–7.64; $P < .001$; absolute risk, 4.1% [5 new cases for 100 patients treated]).⁹

METHODOLOGY AND DATA SOURCE

To determine the economic burden of down-dosing and discontinuation after ibrutinib start, a research team from Milliman analyzed 2015-2019 data from a proprietary Medicare Advantage claims database that contains annual enrollment information and all Parts A, B, and D claims for approximately 2.5 million annual members.¹ The index years for the analysis were identified as 2016, 2017, and 2018, with 2015 used as a “look back” year for 2016 index cases and 2019 used as a “look forward” year for 2018 index cases.¹

Patients enrolled for at least 1 month in Medicare Advantage medical and Part D coverage who were at least 18 years of age and who had 2 or more qualified, CLL/SLL-coded claims (≥ 7 days; ≤ 6 months apart) between 2016 and 2019 were identified as the CLL/SLL study population.¹

From this population, patients who filed at least 2 prescription claims with an ibrutinib National Drug Code between 2016 and 2019 were identified as ibrutinib users.¹

New ibrutinib users were identified as patients from this group who did not fill a prescription for another BTK inhibitor before the first ibrutinib claim (ie, the index date) and who had a qualified CLL/SLL claim on or before the index date. To be eligible for inclusion in the investigators’ analysis, new users were required to have had 12 months of continuous Medicare Advantage Part D enrollment before and after the index date. Eligible patients who filled a second prescription for ibrutinib within 60 days of the index date and who did not fill a prescription for another BTK inhibitor during that time were identified for the investigators’ 12-month post-ibrutinib episode analysis.¹

Key Metrics Analyzed

In the group identified for analysis, investigators examined rates of and average time to discontinuation, down dosing, and AEs, as well as total health care costs accumulated in the 12 months following ibrutinib start. Using these key metrics, investigators then compared patients who newly experienced AF (new AF) during the episode period with those who did not experience new AF during this period.¹

During the episode period, patients who did not fill a prescription for ibrutinib for at least 60 days were considered to have discontinued therapy. Those who filled a new prescription for a lower average daily quantity of ibrutinib during the episode period were defined as having down-dosed. AEs were defined as conditions or events potentially related to ibrutinib use, with “new” AEs being coded during the episode period but not during the 12-month period prior to ibrutinib start (baseline). The investigators identified patients with AF as those who had at least 1 qualified claim that included a coded diagnosis with AF/flutter in any position on the claim.¹

The amount paid by the Medicare Advantage Part D plan plus patient cost-sharing constituted allowed health care costs. To calculate average annual allowed costs by service, investigators totaled all

allowed costs for that service during episode periods and divided by the number of patients in the study cohort.¹

RESULTS

A total of 15,017 patients made up the CLL/SLL population. Of these, 1568 were identified as ibrutinib users. In all, 404 individuals were new ibrutinib users, and 355 patients ultimately met all eligibility criteria and were analyzed. Of the analyzed group, 61% were male (average age, 76.3 years).¹

Treatment Patterns and Adverse Effects

Of the analyzed cohort, 28% discontinued ibrutinib within the episode period (average time after starting ibrutinib, 3.8 months). During the period, 25% of the cohort down-dosed (average time after starting ibrutinib, 4.4 months).¹

Within the cohort and during episode period, AF was the most frequent of new AE conditions identified following initiation of ibrutinib therapy (Table 1).¹ Of analyzed patients who also had Medicare Advantage Part D eligibility for at least 1 year before the baseline period, 2.2% (4 of 185 patients who had eligibility) experienced new AF during the baseline period. Of all analyzed patients, 13.5% (48 of 355 patients) experienced new AF during the episode period. This difference in incidence rates was statistically significant ($P < .0001$).¹

Subpopulation Analysis: Outcomes, Treatment Patterns, and Costs Among Patients With New AF

Employing the same key metrics used for analysis of the overall study group, investigators compared patients who experienced new AF during the episode period ($n = 48$) with patients who did not experience new AF during the episode period ($n = 307$). The groups were similar in average age (new AF, 77.4 years; no new AF, 76.1 years) and sex (new AF, 60.4% male; no new AF, 61.2% male).¹

New AF occurred throughout the first 11 months (average onset after starting ibrutinib, 5.4 months). During the episode period, patients with new AF had a significantly higher rate of ibrutinib discontinuation than did those without new AF (54.2% vs 24.1%, respectively; $P = .0002$) (Table 2).¹ Most patients with new AF who discontinued (73%) did so after the first AF episode. Patients with new AF down-dosed at a rate similar to that of those without new AF (25% vs 24%, respectively).¹

Of patients with new AF, 50% had at least 1 inpatient admission within 30 days of first AF episode; of these admissions, 42% were for cardiac arrhythmias. Compared with those without new AF, patients with new AF were approximately 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 a stay for observation, and 4.3 times more likely to have a skilled nursing facility admission. All rates were significantly higher for the new AF population than for the rest of the study cohort ($P < .05$) (Figure).¹

Non-ibrutinib average annual allowed costs, which included all plan-paid amounts plus cost sharing for hospital, professional, non-ibrutinib drug, and other expenses, were approximately

Table 1. Adverse Events Before and During 12-Month Episode Period: Conditions¹

AEs	Patients coded with AEs during baseline period, ^a %	Patients with new AEs (episode period ^b only), %	Patients in AE group who DD ibrutinib within 2 months of first new AE, ^c %	Patients in AE group who DC ibrutinib within 2 months of first new AE, ^c %
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	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

AEs, adverse events; AF, atrial fibrillation; DC, discontinued; DD, down-dosed.

^a Baseline period is the 12-month period before ibrutinib index date. The incident rate of new AF in the baseline 12 months prior to ibrutinib start was 2.2%, which was statistically significant ($P < .0001$).

^b Episode period is the 12-month period after ibrutinib index date. The incident rate of new AF in the 12 months following ibrutinib start was 13.5%, which was statistically significant ($P < .0001$).

^c New AEs are defined as those first observed during the episode period and not during the baseline period.

Table 2. New AF Subpopulation Analysis Demographics and Treatment Patterns^{1,a,b}

Metric	Patients with no new AF	Patients with new AF	P values
Total patients	307	48	—
Average age, y	76.1	77.4	—
Male patients, %	61.2	60.4	—
Patients who DC ibrutinib, %	24.1	54.2	.0002
Patients who DC ibrutinib within 2 months of first AF occurrence, %	—	36.4	—
Average ibrutinib use, mo^c	10.6	8.8	.0018

AF, atrial fibrillation; DC, discontinued; mo, month(s); y, year(s).

^a New AF is defined as first observed during the 12 months after, but not during the 12 months before, ibrutinib start.

^b Down-dosing and discontinuation were observed for the specified months after the first AF occurrence.

^c Average months of ibrutinib use may include resumed periods for those who discontinued ibrutinib.

1.75 times higher for patients with new AF during the episode period than for patients without new AF (\$48,250 vs \$27,574, respectively; $P < .0001$). Additionally, patients with new AF who discontinued treatment had significantly higher non-ibrutinib costs than did patients with new AF who continued treatment (\$59,265 vs \$35,232; $P = .019$) (Table 3).¹

CONCLUSIONS

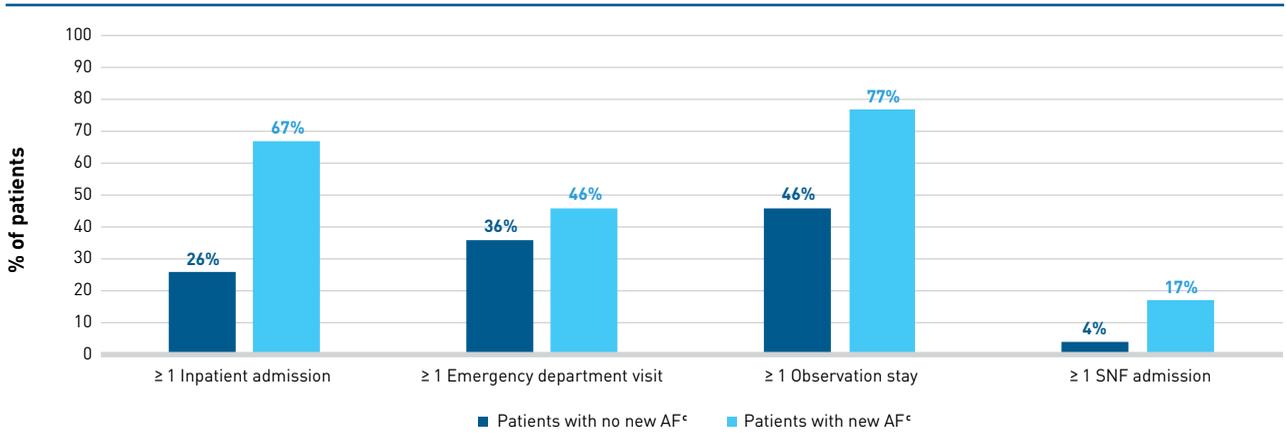
Results from this claims-based analysis demonstrated that patients with CLL/SLL who experienced new AF within the first 12 months of starting ibrutinib therapy had significantly higher rates of ibrutinib discontinuation and higher health care resource utilization rates as

well as significantly increased average non-ibrutinib health care costs during that period when compared with those who did not experience new AF. The investigators noted that new BTK inhibitors are emerging that may address the high rates of AEs (eg, AF) that commonly are seen in patients with CLL/SLL who newly start ibrutinib.

LIMITATIONS

The results presented here are based on Milliman's analysis of the Milliman proprietary Medicare Advantage Parts A, B, and D data (2015-2019). Use of different data sets, time periods, and methodologies may produce different results. Claims-based analyses reflect provider coding, which may not capture all health care utilization.

Figure. Percentages of Patients With CLL/SLL Utilizing Medical Services During 12 Months After Ibrutinib Start^{1,a,b}



AF, atrial fibrillation; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; SNF, skilled nursing facility.

^a At least 1 admission, visit, or stay constitutes use of the service.

^b Patients with new AF were significantly more likely to utilize each of these services compared with those with no new AF ($P < .05$).

^c New AF is defined as first observed during the 12 months after but not during the 12 months before ibrutinib start.

Table 3. Average Annual Cost per Patient in Ibrutinib CLL/SLL Episode Population With and Without New AF^{1,a,b,c}

Metric	Patients with no new AF	Patients with new AF ^d	Continuing users with new AF	Discontinuers with new AF ^e
Number of patients	307	48	22	26
Average months on ibrutinib	10.6	8.8	12.0	6.1
Total cost of care	\$156,871	\$153,710	\$196,153	\$117,796
Ibrutinib, Medicare Advantage Part D^f	\$129,296	\$105,460	\$160,921	\$58,531
Total non-ibrutinib costs:	\$27,574	\$48,250	\$35,232	\$59,265
Inpatient hospital	\$4458	\$12,604	\$9348	\$15,359
Outpatient hospital	\$10,832	\$12,807	\$7493	\$17,303
ED/Observation	\$785	\$1452	\$956	\$1871
Professional	\$7206	\$11,058	\$10,738	\$11,329
SNF/Home health/Hospice	\$923	\$2763	\$1439	\$3884
Chemotherapy administration	\$203	\$503	\$64	\$874
Medicare Advantage Part B chemotherapy	\$3484	\$5976	\$1679	\$9612
Other Medicare Advantage Part B drugs	\$4112	\$4311	\$3852	\$4700
Medicare Advantage Part D chemotherapy	\$537	\$1774	\$0	\$3276
Other Medicare Advantage Part D drugs	\$3153	\$6330	\$5366	\$7145

AF, atrial fibrillation; ED, emergency department; SNF, skilled nursing facility.

^a During the 12 months after ibrutinib start

^b New AF is defined as first observed during the 12 months after but not during the 12 months before ibrutinib start.

^c Costs reflect allowed expenditures that include plan paid amounts plus patient cost sharing. Medicare Advantage Part D costs are total allowed reimbursement, including coverage gap and catastrophic coverage period amounts, and do not represent the amount for which the Medicare Advantage enrollment with medical and Part D coverage plan is liable. Costs have been trended to 2019 using the Milliman health cost guidelines.

^d Non-ibrutinib cost differences between patients with and without new AF are statistically significant ($P < .0001$).

^e In patients with new AF, non-ibrutinib cost differences between those who continue and discontinue ibrutinib use are statistically significant ($P = .0185$).

^f Bruton tyrosine kinase inhibitors are reflected in "Ibrutinib, Medicare Advantage Part D" service line, not in "Medicare Advantage Part D chemotherapy."

New AE identification is based on no coding of the AE during the 12-month baseline period before initiation of ibrutinib therapy; further, it does not capture AE coding prior to the baseline period. Code sets for identification criteria are available upon request.¹ •

DISCLAIMER: This presentation summarized in this *AJMC*® Product Theater Recap was commissioned by BeiGene, USA, which manufactures the BTK inhibitor zanubrutinib. The findings and conclusions summarized here reflect the opinion of the authors of the presentation; Milliman, Inc. does not endorse any policy or product. If this presentation is reproduced, Milliman requests that it be reproduced in its entirety, as pieces taken out of context can be misleading.

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Insights From the Principal Investigator: an Interview With Kathryn Fitch, MEd, RN

An editor from *The American Journal of Managed Care*® (AJMC®) spoke with Kathryn Fitch, MEd, RN, about the results of the real-world analysis of the incidence of adverse effects (AEs) and related economic costs in patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) treated with ibrutinib. Fitch is a principal and health care management consultant at Milliman, Inc.

AJMC®: Treatment with ibrutinib has been the preferred first-line regimen for patients with CLL/SLL for many years. During this time, we have learned a lot about its efficacy and associated AEs. Going into your analysis, what was known about ibrutinib?

Fitch: Ibrutinib, a first-generation BTK [Bruton tyrosine kinase] inhibitor, was approved in 2016 for first-line treatment of CLL. It has greatly improved the outcomes for patients with CLL.

However, ibrutinib use—like use of second-generation BTK inhibitors—is associated with particular AEs. Some patients experience mild to moderate AEs—such as GERD [gastroesophageal reflux disease], diarrhea, fatigue, and headaches—which typically don't lead to discontinuation of ibrutinib. On the other hand, some patients experience more serious AEs—such as AF [atrial fibrillation], heart failure, and, in rare cases, heart attack and stroke; this often leads to discontinuation of ibrutinib.

AJMC®: In your analysis, which AEs associated with the use of ibrutinib stood out to you?

Fitch: Using our proprietary Medicare Advantage claims data, we analyzed patients with CLL/SLL who newly started ibrutinib. Regarding the more serious AEs, 13.5% of this population developed new AF, and 12.7% developed new heart failure within 12 months of starting ibrutinib. Milder AEs also were noted; 21.1% of patients had a claim coded with diagnosis of arthralgia/myalgia, and 13.2% of patients had a claim coded with diagnosis of GERD, in the 12 months after starting ibrutinib and after not having had a claim coded with diagnosis of these conditions in the 12 months prior to starting ibrutinib.

AJMC®: Patients who developed new AF did so, on average, 5.4 months after starting ibrutinib, with new development

... 50% of those who newly developed AF [atrial fibrillation] had at least 1 inpatient admission within 30 days of their first AF occurrence ...

of AF continuing among the population over the first 11 months. Did duration of new ibrutinib use correlate with onset of new AF?

Fitch: Not really. Thirty-three percent of patients who newly developed AF did so within the first 3 months of starting ibrutinib. However, after that 3-month period, development of new AF occurred throughout the remaining 12 months that we followed patients.

AJMC®: Did anything surprise you about this subpopulation who developed new AF after starting ibrutinib?

Fitch: Yes! Although occurrence of new AF wasn't a surprise, it was a bit higher than we expected. But, most significantly, 50% of those who newly developed AF had at least 1 inpatient admission within 30 days of their first AF occurrence, and 42% of those admissions were for cardiac arrhythmias.

Another surprise was the higher cost during the 12 months after ibrutinib start for patients who newly developed AF compared with those who did not newly develop AF. Also, for those who developed AF, 36.4% discontinued ibrutinib within 2 months of their first AF occurrence; this inability to continue treatment can indicate a quality-of-care issue.

AJMC®: What might these findings mean for health care decision-makers working in managed care?

Fitch: Among patients who developed new AF after starting ibrutinib, the discontinuation rate of ibrutinib and the incidence

of inpatient admissions were high following the first occurrence of the condition. Moreover, new ibrutinib starters who developed new AF had \$21,000 higher average non-ibrutinib costs in the 12 months after starting ibrutinib compared with those who did not develop new AF (\$48,000 vs \$27,000, respectively). The patients with new AF had a higher rate of inpatient hospital admissions which, along with higher professional and post-acute care service utilization, drove much of these higher costs.

AJMC®: In the presentation, you noted that your team is performing the same analysis on another data set of 35 million lives annually. What can you tell us about this study?

Fitch: The first analysis—which we’ve been discussing in this interview—used Medicare Advantage data. Forty percent of Medicare beneficiaries are now enrolled in a Medicare Advantage plan. The analysis that we performed examined about 2.5 million Medicare Advantage lives, which is about 10% of the Medicare Advantage population.

In this next analysis, we are analyzing Medicare fee-for-service data, which represent 60% of the approximately 60 million Medicare beneficiaries in the United States.

We are creating a research brief to report the findings of the Medicare fee-for-service analysis. Thus far, most of the outcomes are very similar between the Medicare Advantage and Medicare fee-for-service populations. For instance, within the subpopulation of patients with CLL/SLL who started ibrutinib, the percentage of patients who developed new AF

is very similar. However, there were a few differences, which we will highlight in the soon-to-be-published research brief.

AJMC®: What was the aim of this second analysis?

Fitch: Our interest was in comparing key metrics for new ibrutinib starters in the Medicare fee-for-service population with those in the Medicare Advantage population. We know that the cost profile between these populations will be slightly different because of differences in fee schedules. But, specifically, we wanted to identify if incidence rates of AEs and ibrutinib discontinuation patterns varied between these populations.

AJMC®: How might future research investigate the cost of ibrutinib?

Fitch: We were only able to look at ibrutinib because we only had data through 2019. In November 2019, acalabrutinib, a second-generation BTK inhibitor, was approved for treatment of CLL/SLL. And so now, we have Medicare Advantage Part D data from 2020 and the first three quarters of 2021 that we can use to compare patterns of AEs among patients newly starting acalabrutinib with patterns among those newly starting ibrutinib. Another second-generation BTK inhibitor, zanubrutinib, was also approved in November 2019, for the treatment of mantle cell lymphoma. We also plan to compare patterns of AEs among patients newly starting zanubrutinib with those newly starting ibrutinib. •

Payer and Health Systems Perspective: an Interview With Michael Kolodziej, MD, FACP

An editor from *The American Journal of Managed Care*® (AJMC®) spoke with Michael Kolodziej, MD, FACP, about a recent claims-based analysis of the use of ibrutinib for the treatment of chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), the resulting adverse events (AEs), and the related economic costs. Kolodziej is a medical oncologist and senior advisor at ADVI Health.

AJMC®: Treatment with ibrutinib has been the preferred first-line regimen for treatment of patients with CLL for many years. How did the introduction of this BTK [Bruton tyrosine kinase] inhibitor change the way that patients seek and receive care?

Kolodziej: If we look back at the introduction of ibrutinib—initially in relapsed disease and then subsequently in first-line therapy, and then initially in high-risk disease and then subsequently in all patients—ibrutinib was transformative. It has been proven highly effective and generally well tolerated. The biggest negative, in my opinion, particularly from a payer perspective, is that it's expensive. The use of ibrutinib was also an open-ended proposition: as with many oral cancer drugs that are not believed to be curative—patients may be on them for many years—its cumulative cost can be substantial.

Ibrutinib also had a pretty good safety profile in clinical trials; however, as is almost invariably the case with all treatments, the full toxicity profile was better elucidated when it was used in the real world, and that is what we are going to talk about today. It was recognized from the original clinical trials that the use of ibrutinib was associated with dysrhythmias, particularly atrial dysrhythmias. It was associated with hypertension, bleeding problems, and other AEs. However, it's taken us a little while to recognize the clinical and economic consequences of many of those AEs.

First, many of these AEs are of consequence because there's a cumulative risk of toxicity. Patients can be treated with ibrutinib for a long time, and, during that time, their risk of AEs increases. Second, some of these AEs can lead to the need to discontinue treatment. This means that whatever clinical benefit the patient was experiencing becomes irrelevant. Both of these events create costs for the health care system. Atrial dysrhythmia is an excellent example, because new onset AF

The information [in this study] can help the health plan to predict what's going to happen to their managed-care population and to understand what optimal care for that patient might look like.

[atrial fibrillation] triggers a certain chain of clinical events with associated costs and implications for the patient.

The BTK inhibitors are great. The first generation, which is ibrutinib, was transformative, and now we're seeing the introduction of second- and subsequent-generation BTK inhibitors. It's only a matter of time before we have multiple second-generation BTK inhibitors that are available to us.

AJMC®: How do the results from real-world analyses like this one help to inform formulary decision-making?

Kolodziej: Real-world evidence helps us contextualize clinical trial results. Patients who enter clinical trials are not necessarily representative of patients who are treated in the real world. Real-world evidence is extremely beneficial to providers. For them, it answers questions such as, "Is this treatment really going to work that well?" and "What are the hidden problems that may occur?"

In the traditional payer world, though, it's hard to use real-world evidence to manage formulary placement. Most payers don't have the power to make binary cover/don't-cover decisions. Payers can prefer 1 agent over another within the formulary through, for example, the use of clinical pathways programs. It's also theoretically possible to use step therapy to accomplish the same thing, but that isn't done all that often, and you need a tremendously compelling story to do it.

That said, we now have hybrid entities such as integrated delivery networks [IDNs]. Kaiser Permanente is an IDN that most people think of, but there are many others. IDNs have a lot more power in terms of formulary management and

partnering with providers to be more prescriptive about preferred agents. For IDNs, real-world data are priceless. IDNs focus on total cost of care. They're not as beholden to some of the regulatory requirements about protected classes. Therefore, they can focus on delivering what they believe to be the single best therapy—if there is a single best therapy—for their patient population.

Traditionally, I would say real-world evidence has been good for providers, but it rarely results in formulary changes. Today, however, IDNs are changing that binary paradigm.

AJMC®: The results of this analysis revealed that within 12 months of starting ibrutinib treatment, both patients who experienced new AF and those without new AF down-dosed at similar rates (25% and 24%, respectively). How does down-dosing of treatment impact health care resource utilization?

Kolodziej: Payers are sensitive to the downstream effects associated with toxicity that can interrupt optimal care. Down-dosing, or any other therapeutic change that could compromise clinical outcomes, is a problem for the health plan. Payers aren't ignorant of the cost of continuing the drug, but, I assure you, they don't want patients in the hospital. In addition, the plan doesn't want patients to have to move on to the next line of therapy, because it's rare that the next line of therapy is a better option for the patient than the preferred line of therapy. This is why payers view down-dosing as a negative event.

AJMC®: Patients with new AF had a significantly higher rate of ibrutinib discontinuation in the 12 months after starting ibrutinib than did those without new AF ($P = .0002$). How could these results help inform payers or providers?

Kolodziej: I'm not sure it directly informs formulary decision-making. The results are much more impactful in making providers sensitive to the adverse health consequences of this AE.

Theoretically, the health plan could use this information to facilitate a treatment change, as required, should the toxicity develop. Knowing that a patient who experiences AF has a pretty good chance of having to discontinue therapy might encourage the health plan to pay attention to this patient. The

patient might require a smoother transition to the next therapy, whether it be an alternative BTK inhibitor or something else. This information can help the health plan to predict what's going to happen to their managed-care population and to understand what the optimal care for that patient might look like.

AJMC®: A total of 87% of patients *did not* experience new AF in the 12 months after starting ibrutinib. What do these results tell you?

Kolodziej: Yes, that's what the clinical experience has been: many patients do extremely well on treatment with ibrutinib. However, this study analyzed claims data for a Medicare population of older adults. [The average age of the ibrutinib CLL/SLL episode cohort was 76.3 years.] Most older adult patients have comorbidities. We do not want these patients to experience AF. If you said to a provider that AF occurs in 10%, 12%, or 15% of patients with ibrutinib, before writing that prescription, they will likely want to ensure that patient has the greatest likelihood of benefitting [from the treatment] and the lowest likelihood of experiencing an AE. To that end, the incidence rate gleaned from this analysis is an important piece of knowledge.

AJMC®: Average annual non-ibrutinib costs were significantly higher for patients who experienced new AF in the 12 months after starting ibrutinib and for patients with new AF who discontinued ibrutinib.^{1,a} How might these findings inform understanding of the costs associated with ibrutinib among patients who experience new AF after starting treatment?*

Kolodziej: Let's say you're a provider, and you have a patient being treated with ibrutinib, and they walk into your office. They're a little short of breath, and they have new AF. That patient is likely going to the hospital for a week. New onset AF means the patient is going to the hospital, and they are going to have an echocardiogram and be admitted to the telemetry floor. One thing will follow another thing, and those things cost a lot of money.

This study used claims data—real-world data. The claims likely underestimate other problems. Those other problems may or may not be associated with significant health outcomes

*Patients who experienced new AF had significantly higher non-ibrutinib average annual allowed costs after ibrutinib start (\$48,250) compared with those without new AF (\$27,574; $P < .0001$). Patients who experienced new AF who discontinued ibrutinib had significantly higher average annual non-ibrutinib costs (\$59,265) compared with patients who experienced new AF who didn't discontinue ibrutinib (\$35,232; $P = .0185$).¹

or health care expenses, but we should not be surprised that the non-drug-associated costs of new onset AF are high. If you have ever lived through that experience, you know exactly what's going to happen to that patient.

AJMC®: How might this study help an IDN or a health plan make treatment and coverage decisions based upon the total costs of care presented?

Kolodziej: Over the years, a common complaint of biopharmaceutical companies—life science companies, in fact—has been that we don't really understand the total cost of care. And that's fair; that's a true statement. The reason is that all that information lies within the claims data, and the health plans own that data. Many are not that interested in sharing that data. However, if you're an IDN, you are an at-risk entity. To succeed, you must control both the quality and the cost of care. IDNs need to pay attention to this, because they are at risk as an organization. This information is critical for them to succeed as business units, as entities.

ACOs [accountable care organizations], which are also at-risk entities, need to pay similar attention to the cost of the treatment as well as to any costs or adverse health outcomes that are associated with that treatment. To succeed as an ACO or an IDN, you must be able to appropriately manage sick patients. To this end, ACOs are becoming more sophisticated.

If you're managing a population of patients with CLL, you're going to look at the cost of treatment. You'll look at the pharmacy cost—which, arguably, is the largest cost for these patients—but also at the medical cost, and that's why we're talking about this AF situation. ACOs must pay attention to total cost of care. To the extent that they can, they must institute policies that protect the quality of care and that are sensitive to the costs. This different way of thinking becomes possible because of the closer affiliation between the risk bearing entity and the provider. With ACOs, they're both in the same boat.

AJMC®: What else would you want to see from BTK inhibitors as this class evolves?

Kolodziej: There are a few things I'd like to see. One is more real-world data. It's got to come out, and we need to understand it better. It's mind boggling to me that we don't have more of these kinds of studies. They're very, very helpful.

Two, we need to understand whether fixed-duration therapy has a future because of the issue of cumulative cost and

cumulative toxicity. Whether it's fixed-duration [therapy with a] single agent or fixed-duration [treatment with] combination [therapy], what does it mean in terms of efficacy? What does it mean in terms of toxicity? What does it mean in terms of cost? Long ago, I remember arguing about whether you could stop imatinib. We've come a long way in terms of understanding how we manage CML [chronic myelogenous leukemia]. We're going to walk that same path in CLL, I'm quite sure of it.

Three, as time goes on, we are starting to see some resistance to these drugs. Initially, it was not thought to be much of a problem, but it is going to be an issue as we have patients on therapy for a long time. Whether resistance issues are the same with the second-generation [BTK inhibitors] versus the first generation, we don't know yet.

To me, those are the big things. The first is continued accumulation of evidence in the real world regarding efficacy and toxicity, the second is the place of fixed-duration therapy, and then the third is resistance.

AJMC®: What should we keep in mind as we consider this analysis?

Kolodziej: The one thing I would say is this: remember that this is [an analysis of] a Medicare Part D claims data set of patients with an average age of 76 years. However, there are plenty of young people with CLL, and we need to know more about the effects of treatment among patients in that population. This is critically important for commercial health plans. It's also important for employers, because people who have employer-sponsored insurance may have CLL, too. We need to understand the younger set of patients.

The other thing we need to do is start thinking about clinical subsets. Which clinical subsets—by age and comorbidity, for instance—are at higher risk for an AE or other poor outcome? Which clinical subsets are at lower risk? I have a million questions. I won't be around long enough to hear the answers, but there are a million questions. Real-world evidence is exciting, because, finally, all that stuff the doctors had to put up with for electronic medical records may be worth something. That'd be great. •

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