Medication Adherence, Treatment Patterns, and Dose Reduction in Patients with Metastatic Castration-Resistant Prostate Cancer Receiving Abiraterone Acetate or Enzalutamide

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BACKGROUND: The efficacy of and overall survival associated with metastatic castration-resistant prostate cancer (CRPC) treatments rely on patients’ consistent adherence to the recommended dosage regimens.

OBJECTIVES: To evaluate treatment patterns and patient adherence to abiraterone acetate or enzalutamide therapy in real-world practice, and to examine the factors that may be associated with medication dose reduction in patients with metastatic CRPC.

METHODS: Retrospective analyses were conducted using the Truven Health MarketScan research databases among patients with metastatic CRPC who initiated treatment with abiraterone acetate or enzalutamide between October 1, 2012, and December 31, 2014 (index date). The patients were followed for up to 12 months, and their baseline characteristics were assessed during the 6 months before the index date. Medication adherence was measured at 3, 6, 9, and 12 months postindex using medication possession ratios (MPRs), and dose reduction was measured using refill gaps and relative dose intensity over the entire observation period. Kaplan-Meier survival analyses and Cox proportional hazards models were used to assess the association between the initial treatment and the risk for dose reduction.

RESULTS: The study included 2591 and 807 patients who initiated treatment with abiraterone acetate and enzalutamide, respectively. At 6, 9, and 12 months postindex, the patients who initiated abiraterone acetate had higher MPRs than the patients who initiated enzalutamide. In addition, the patients who initiated abiraterone acetate had lower Kaplan-Meier rates of dose reduction across 4 measurements for dose reduction. All hazard ratios for treatment (abiraterone acetate vs enzalutamide) were significantly lower than 1 (range, 0.57-0.80), indicating a lower risk for dose reduction associated with abiraterone acetate.

CONCLUSION: Patients who initiated abiraterone acetate therapy had higher medication adherence and lower risk for dose reduction than those who initiated enzalutamide therapy. Improved medication adherence may be associated with longer duration of treatment, which in turn may lead to better survival. Further research is needed to assess the potential effect of medication adherence on the overall survival of patients with metastatic CRPC.

KEY WORDS: abiraterone acetate therapy, dose reduction, enzalutamide therapy, medication adherence, medication possession ratio, metastatic castration-resistant prostate cancer, proportional hazards, survival, treatment patterns
KEY POINTS

- Treatment options for prostate cancer are expanding and can prolong survival and improve quality of life, but lack of medication adherence remains a concern.
- This retrospective study compares real-world treatment patterns and adherence to abiraterone acetate versus enzalutamide in patients with metastatic CRPC.
- Compared with patients who initiated enzalutamide therapy, initiating abiraterone acetate treatment led to better medication adherence, reflected in higher medication possession ratios (MPRs), greater proportions of MPRs of ≥80%, and lower proportions of medication nonpersistence.
- Patients who initiated abiraterone acetate therapy were less likely to have dose reduction than those initiating enzalutamide therapy.
- Overall, the initial treatment choice, previous use of a corticosteroid, and the presence of a CNS condition during follow-up are potential predictors for dose reduction in this patient population.

and may present as a constant rise of prostate-specific antigen in serum levels, the progression of pre-existing disease, the appearance of new metastases, or any combination of the 3. Once CRPC has spread to other organs or tissues in the body, such as in bone or in the bladder, it is referred to as metastatic CRPC. In recent years, treatment options for advanced prostate cancer have expanded. Prolonged survival rates, pain reduction, and improvement in quality of life have been achieved by using new drugs, such as docetaxel, cabazitaxel, abiraterone acetate, enzalutamide, and sipuleucel-T.

Abiraterone acetate is an androgen biosynthesis inhibitor that was approved in 2011 by the US Food and Drug Administration (FDA) to be used in combination with prednisone as a treatment for patients with metastatic CRPC after previous docetaxel treatment. Enzalutamide, which works by blocking the androgen receptor pathway, was approved by the FDA for the treatment of metastatic CRPC in 2012. Both medications are now approved for a broader indication comprising patients with metastatic CRPC.

Patient medication adherence is critical for effective treatment. Patients who underuse their prescribed medication are likely to experience worsening of their primary condition and the emergence of new comorbid conditions. Dose reductions or discontinuation of a drug, which can lead to a lack of patient adherence to treatment protocols, may have a major impact on patient health and on the healthcare system as a whole. This study compares the utilization of and adherence to abiraterone acetate or enzalutamide in real-world practice in patients with metastatic CRPC, and examines the potential factors that may be associated with medication dose reduction in patients with metastatic CRPC.

Methods

This study used a retrospective longitudinal design. In the main analysis, patients with prostate cancer who initiated abiraterone acetate or enzalutamide therapy between September 1, 2012, and December 31, 2014, were selected to form the study population. The index date was defined as the date of initiation of abiraterone acetate or enzalutamide therapy after September 1, 2012 (ie, right after the FDA approval date for enzalutamide) in a patient who had no evidence of previous use of abiraterone acetate or enzalutamide. Patients were included in the study if they had at least 6 months of continuous eligibility before the index date (ie, the baseline period) and at least 1 diagnosis of prostate cancer (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 185.xx) during the period of continuous eligibility.

The observation period spanned from the index date until health plan disenrollment or the end of data availability, whichever occurred first. For time-to-event analysis, follow-up was censored by the end of the 12-month follow-up. Patients were classified into 2 study cohorts, the abiraterone acetate cohort and the enzalutamide cohort, based on their initial treatment. Because abiraterone acetate was approved for metastatic CRPC in 2011, sensitivity analyses that also included patients initiating abiraterone acetate before September 1, 2012, were conducted.

Data Sources

This study used the Truven Health MarketScan Research databases from January 2010 to December 2014, including separate databases (ie, the Commercial Claims and Encounters database, and the Medicare Supplemental and Coordination of Benefits database) to cover all age-groups; these databases contain claims from employers, health plans, and public organizations. The data in the database comprise service-level claims for inpatient and outpatient healthcare services and outpatient prescription drugs. All census regions are represented in the databases, but the South and North Central (Midwest) regions are predominant.

Outcomes and Statistical Analysis

To evaluate the treatment and adherence patterns in the use of abiraterone acetate or enzalutamide, medica-
tion possession ratio (MPR) and nonpersistence were assessed for all patients at 3, 6, 9, and 12 months after the index date. MPR was defined as the sum of the days of supply of the medication, divided by the number of days between the first fill and the last refill plus the days of supply of the last refill. When prescription fills overlapped (ie, the start date of the refill started before the end of the previous fill’s supply), an adjustment was made such that the prescription start date of the next fill was reset to be the day after the previous fill ended. The proportion of patients with an MPR of ≥80% was also reported. Nonpersistence was defined as a gap of more than 60 days between 2 adjacent refills or between the end of the last refill and the end of the evaluation period.

Dose reduction was assessed using 4 definitions, including (1) a relative dose intensity (RDI) of <85%, where RDI was calculated as the ratio of the delivered dose intensity (ie, dose per unit of time, which was calculated by dividing the total delivered dose by the period over which the total dose was measured) to the standard dose intensity as recommended in the prescribing information of abiraterone acetate or enzalutamide; (2) an RDI of <80%; (3) a refill gap of ≥30 days, where a refill gap was defined as the number of days between a fill plus the days of supply of that fill and the subsequent refill; and (4) a refill gap of ≥60 days. The event date was defined as the date of the last day of supply of the fill before a dose reduction event. Patients who did not have a dose reduction event were censored at the earlier date between their last day of supply from the last refill and the end of the observation period.

Descriptive statistics were used to report the patient and clinical characteristics at baseline and treatment patterns during the observation period. Means, standard deviations (SDs), and medians were used to describe continuous variables; frequencies and percentages were reported for categorical variables. Comparisons between the 2 study cohorts were conducted using the chi-square test for categorical variables and the 2-sided Student’s t-test or Wilcoxon rank sum test for continuous variables, depending on whether the variable was normally distributed.

Kaplan-Meier survival analyses were conducted to illustrate the differences in the distribution of time to dose reduction between patients initiating abiraterone acetate therapy and patients initiating enzalutamide therapy. Kaplan-Meier cumulative probabilities of dose reduction were reported at 3, 6, 9, and 12 months after the index date and were compared between the 2 groups using log-rank tests.

Cox proportional hazards models were used to assess the association between dose reduction (ie, evaluated using the 4 aforementioned definitions) and the initial treatment, as well as other demographic or clinical factors. We conducted 3 Cox proportional hazards models, and reported the hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs).

Model 1 only included the initial treatment (abiraterone acetate vs enzalutamide); model 2 included the initial treatment (abiraterone acetate vs enzalutamide) and potential baseline confounders; and model 3 included the initial treatment (abiraterone acetate vs enzalutamide), potential baseline confounders, and 2 time-dependent covariates that were measured during the observation period.

The baseline confounders included age, region, year of index date, Quan-Charlson comorbidity index at baseline, central nervous system (CNS) conditions at baseline, comorbidities at baseline (ie, diabetes, hypertension, cardiovascular disease, and depression), selected malignant neoplasms at baseline, prostate cancer treatments such as chemotherapy treatments (ie, docetaxel, cabazitaxel, and other chemotherapies), hormonal treatments, sipuleucel-T, radium 223, and corticosteroids (ie, prednisone, dexamethasone, and other corticosteroids). The 2 time-dependent covariates were the presence of a CNS condition diagnosis and the use of medications that may interact with abiraterone acetate or with enzalutamide and were determined according to the prescribing information for the 2 drugs.

Results
A total of 2591 patients who initiated abiraterone acetate therapy and 807 patients who initiated enzalutamide therapy were included in the study population. Compared with patients who initiated enzalutamide, patients who initiated abiraterone acetate were older (mean ± SD, abiraterone acetate vs enzalutamide, 73.8 ± 10.5 years vs 72.8 ± 10.8 years; P = .02), less likely to have previously received chemotherapy (abiraterone acetate vs enzalutamide, 11.5% vs 20.0% for docetaxel; 1.6% vs 4.1% for cabazitaxel; and 14.4% vs 25.2% for other chemotherapies; all P <.001), and more likely to have previously received corticosteroids (abiraterone acetate vs enzalutamide, 54.8% vs 42.6%; P <.0001) at baseline (Table 1, available at www.AHDBonline.com).

Treatment Patterns
Table 2 presents a comparison in the treatment patterns between patients with metastatic CRPC who received abiraterone acetate and those who received enzalutamide. The patients who initiated abiraterone acetate therapy had a longer exposure to treatment, which was calculated as the difference between the day of the first fill and the last day of supply from the last refill for a given treatment (abiraterone acetate vs enzalutamide, mean ± SD, 7.5 ± 6.1 months vs 6.3 ± 5.9 months; P <.0001) relative to the patients who initiated enzalutamide.
Regarding adherence to medication, compared with patients who initiated enzalutamide, the patients who initiated abiraterone acetate had greater MPRs and, accordingly, higher proportions of MPRs of ≥80% (at 6, 9, and 12 months after the index date, respectively; all comparisons had P < .01). In addition, patients who initiated abiraterone acetate therapy had lower proportions of medication nonpersistence, although only the difference for the comparison at 9 months was statistically significant (Table 2).

### Dose Reduction

The Kaplan-Meier estimates of cumulative hazards for dose reduction during a 12-month follow-up indicated that patients who initiated abiraterone acetate therapy had lower rates of dose reduction than patients who initiated enzalutamide therapy (overall log-rank test P < .01 across all 4 definitions for dose reduction; Figure 1). The differences in cumulative rates of dose reduction between treatment groups began to develop 3 months after treatment initiation and were significant (all P < .01) after 9 months of the index date.

The cumulative event rates at 12 months postindex in patients who initiated abiraterone acetate were 20.9%, 9.1%, 24.4%, and 17.8% based on the 4 definitions for dose reduction, respectively (ie, a refill gap ≥30 days, a refill gap ≥60 days, RDI <85%, and RDI <80%), which were systematically lower than those observed in patients who initiated enzalutamide (30.1%, 15.9%, 31.2%, and 24.8%; all P < .01).

Consistently, the results from the Cox proportional hazards models suggested that patients who initiated abiraterone acetate had a lower risk for dose reduction than patients who initiated enzalutamide, with all the crude and adjusted HRs for treatment (abiraterone acetate vs enzalutamide) significantly lower than 1 (Figure 2).

The multivariate Cox model analysis results for dose reduction measured with RDI <85% suggest that patients were less likely to have a dose reduction if they initiated abiraterone acetate (vs enzalutamide, HR, 0.80; 95% CI, 0.66-0.96), were middle-aged (ie, 55–64 years vs ≥75 years, HR, 0.73; 95% CI, 0.58-0.92), were from the Northeastern United States (vs unknown region, HR, 0.48; 95% CI, 0.23-1.00), were receiving prednisone before the initiation of abiraterone acetate or enzalutamide (HR, 0.83; 95% CI, 0.69-0.99), or were without a diagnosis for a CNS condition during follow-up (HR, 0.70; 95% CI, 0.56-0.86). Similar predictors were found when the other definitions for dose reduction were used in the analysis.

By including all patients who received abiraterone acetate in the sensitivity analyses, similar results to those observed in the main analyses (ie, including only patients who initiated abiraterone acetate or enzalutamide therapy after September 1, 2012) regarding treatment patterns, time to dose reduction, and predictors of dose reduction were observed.

### Discussion

This observational study evaluated the treatment patterns and dose reduction associated with abiraterone acetate and enzalutamide therapy in patients with metastatic CRPC based on a large claims database. The results suggest that fewer patients who initiated abiraterone therapy...
acetate therapy had dose reduction during follow-up than those who initiated enzalutamide therapy. The Kaplan-Meier survival curves further illustrate that the lower risk for dose reduction in patients who initiated abiraterone acetate therapy (vs enzalutamide) became noticeable at 3 months of follow-up and were more pronounced during longer follow-up periods.

Two multivariate Cox proportional hazards models were used to estimate the association between the initial treatment with either agent and the risk for dose reduction. Both models indicated that initiating abiraterone acetate therapy was associated with a lower risk for dose reduction than initiating therapy with enzalutamide in patients with metastatic CRPC. Consistent results were obtained using different definitions for dose reduction, indicating that the study results are robust regarding the measurement used for dose reduction.

Moreover, the results show that the initiation of abiraterone acetate, the use of prednisone before abiraterone acetate or enzalutamide treatment initiation, and not being diagnosed with a CNS condition during follow-up were associated with a lower risk for dose reduction. Furthermore, compared with patients who initiated abiraterone acetate therapy, a larger proportion of patients who initiated enzalutamide therapy received chemotherapy previously; this disparity, however, did not have an impact on the difference in risk for dose reduction between the 2 study cohorts.

Our study results for medication adherence to abiraterone acetate therapy are consistent with the MPRs reported by Lafeuille and colleagues, who also used the Truven Health Analytics MarketScan database in their analyses. However, this disparity, however, did not have an impact on the difference in risk for dose reduction between the 2 study cohorts.

Our study results for medication adherence to abiraterone acetate therapy are consistent with the MPRs reported by Lafeuille and colleagues, who also used the Truven Health Analytics MarketScan database in their analyses. Although that study was conducted during an earlier period (ie, December 2010-August 2012), which was before the FDA approval of enzalutamide, the MPR findings on abiraterone acetate therapy of the 2 studies...
are very similar (with a mean MPR of approximately 95% across all assessment time points), suggesting that patients who initiated abiraterone acetate therapy had consistently high medication adherence over time.

The higher rate of dose reduction in patients who initiated enzalutamide therapy (vs abiraterone acetate) observed in our study may be in part explained by the increased risk for fatigue associated with enzalutamide that was reported in clinical trials. The phase 1/2 study of enzalutamide also reported that the most common adverse event with enzalutamide was dose-dependent fatigue, which resolved after dose reduction. By contrast, abiraterone acetate was shown to be associated with a significant improvement in fatigue intensity in patients with metastatic CRPC who had previously received docetaxel. Therefore, in our current study, patients who initiated enzalutamide therapy might have had fatigue events, which in turn might have resulted in decisions related to dose reduction during the treatment period. Moreover, the higher rate of dose reduction observed in patients who initiated enzalutamide versus abiraterone acetate therapy might also be driven by the recommendations for patient management listed in the prescribing information for the 2 medications. The prescribing information for enzalutamide recommends that patients may reuse enzalutamide at the same dose or at a reduced dose after experiencing a grade 3 or worse toxicity or an intolerable adverse event.

### Figure 2

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<th>Hazard Ratios Associated with Dose Reduction in Patients Initiating Abiraterone Acetate or Enzalutamide During a 12-Month Follow-Up Period</th>
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**NOTE:** Estimates of hazard ratios associated with dose reduction were evaluated using 4 definitions among patients with metastatic castration-resistant prostate cancer who initiated abiraterone acetate or enzalutamide over a 12-month follow-up period. A hazard ratio lower than 1 indicates that patients who initiated abiraterone acetate have a lower risk for dose reduction than patients who initiated enzalutamide. **HR** indicated hazard ratio.
enable side effect. The prescribing information for abiraterone acetate recommends considering dose reduction in patients with baseline moderate hepatic impairment or in patients who have hepatotoxicity during treatment.

However, regardless of whether the dose reduction resulted from a patient nonadherence to therapy, patients not receiving their medications on time, or other clinical reasons (ie, the medication was stopped or reduced to manage toxicity), our study showed that compared with patients who initiated abiraterone acetate therapy, patients who initiated enzalutamide therapy had greater reductions of the drug’s dosage than we would expect based on the prescribing information.

To our knowledge, this is the first study to assess and compare the treatment patterns of and adherence to abiraterone acetate and enzalutamide in real-world settings. The use of different measures for medication adherence, the use of alternative definitions for dose reduction, and the assessment of adherence at different time points during follow-up contribute to the robustness of our study’s results.

Limitations
As with all claims databases, the Truven Health MarketScan research databases are subject to billing inaccuracies or the incomplete coding of diagnoses. Because no information was available in pharmacy claims to assess whether the medication was taken as prescribed, the results of this study may overestimate the actual consumption of the medications.

In addition, because of the limitations in ICD-9-CM coding specificity, the verification of a metastatic CRPC diagnosis was not possible.

Moreover, as with all observation studies, our results may be subject to residual confounding factors because of unmeasured confounding factors, such as the potential difference in patients’ disease states that may confound the observed association between treatments for metastatic CRPC and dose reduction.

Nevertheless, health insurance claims data remain a valuable source of information, because they constitute a fairly valid large sample of patients’ characteristics and outcomes in a real-world setting.

Conclusions
This retrospective study showed that patients who initiated abiraterone acetate therapy had greater medication adherence and a lower risk for dose reduction compared with patients who initiated enzalutamide therapy.

The attempt to identify potential predictors for dose reduction should motivate further investigation in this area. In addition, as high-deductible health plans are becoming more pervasive, and the costs associated with the treatment of metastatic CRPC are high, future studies may be conducted to assess the potential impact of patients’ out-of-pocket expenses on medication adherence to treatments of metastatic CRPC. Because treatment with abiraterone acetate or with enzalutamide can prolong survival in patients with metastatic CRPC, and longer duration of treatment may be associated with longer survival, our findings suggest that patients who initiate abiraterone acetate may have a better survival rate, lower rates of healthcare resource utilization, and lower healthcare costs than patients who initiate enzalutamide therapy. Future studies should be conducted to confirm these hypotheses.

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Author Disclosure Statement
Dr Behl is an employee and stockholder of Johnson & Johnson. Dr Ellis is an employee of Janssen Scientific Affairs, and a stockholder of Johnson & Johnson. Mr Pilon, Dr Xiao, and Mr Lefebvre are employees of Analysis Group, which received a research grant from Janssen Scientific Affairs.

References
A First Step Toward Improving the Complex Approach to Metastatic Prostate Cancer Management

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**PATIENTS:** According to the American Cancer Society, there will be more than 161,000 new cases of prostate cancer diagnosed in 2017.¹ This makes prostate cancer the most common cancer diagnosed in men, and it is second only to breast and lung cancers as the most frequently diagnosed solid-organ cancer.¹

**PAYERS:** The total US cost of prostate cancer care was almost $12 billion in 2010, more than $14 billion in 2016, and is projected to be more than $16 billion by 2020.²³ The majority of the cost of caring for prostate cancer is in the outpatient setting, making it a significant issue for US payers.⁴

The launch of abiraterone acetate in 2011 and of enzalutamide in 2012 expanded the treatment options for those patients who had metastatic castration-resistant prostate cancer. Both medications are costly, and payers generally manage access to these agents using strategies such as prior authorization, the use of specialty pharmacy, and managing adherence and compliance using medication therapy management approaches. However, little is known about the effectiveness of such programs, and how these medications are actually taken by patients in a real-world setting.

In this article, Behl and colleagues conducted a large database study of patients with metastatic castration-resistant prostate cancer who were being treated with abiraterone acetate or with enzalutamide.⁵ They concluded that “patients who initiated abiraterone acetate therapy had higher medication adherence and lower risk for dose reduction than those who initiated enzalutamide therapy.”⁵

**RESEARCHERS:** This real-world analysis is a good first step for payers as they consider their management strategies for this group of patients. However, it creates more unanswered questions that will be important for future research, such as:

1. Does the difference in real-world adherence have an effect on outcomes for these patients?
2. What is the ultimate cost impact of this difference in adherence, especially if there is an effect on outcomes?
3. Are there patient characteristics that can be used to predict nonadherence to these therapies, and how can payers use these parameters to better manage access to therapy?
4. How can payers use such data to improve outcomes and access to care for these patients?

In general, this is the type of research that will become increasingly important to payers as they struggle to manage the growing cost of treating prostate cancer. Although this study does not answer the questions above, it is a good first step toward improving the management of a complex and costly therapeutic space.

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