BRIEF REPORT

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Real-world Duration of Use and Dosing Frequency of Daratumumab in Patients With Multiple Myeloma in the United States

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Abstract

Daratumumab (DARA) is an anti-CD38 monoclonal antibody approved as a combination therapy for newly diagnosed multiple myeloma (MM) and as monotherapy and combination therapy for relapsed or refractory MM cases. We assessed the length of DARA use across lines of therapy and the probabilities of treatment discontinuation in patients with MM in the real-world. We used the deidentified Clinformatics Data Mart database from Optum to identify patients with MM (n=2124) who received DARA-containing treatment between November 1, 2015 and March 31, 2021 in the United States. Patients were excluded if they had received a stem cell transplant. The duration of DARA use was defined as the time interval between the first initiation and discontinuation of DARA as a time-to-event outcome using the Kaplan-Meier method. A gap of more than 60 days between 2 consequent DARA claim dates was defined as DARA discontinuation. The median duration of continuous DARA use was 16.6 months. By 24 months, 33.1% of patients remained on DARA treatment. In a subgroup analysis of patients with 12 months or more continuous insurance coverage (n=1246), the median length of DARA use was 24.7 months; by 24 months, 51.8% remained on DARA treatment. The dose adherence ratios (observed DARA doses relative to the label) were close to 1.0, particularly among patients with longer follow-up, indicating that real-world DARA dosing frequency was similar to that on the approved label. In summary, this real-world analysis reported that the median duration of continuous DARA use is 16.6 months, with high dosing adherence in patients who have MM.

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Multiple myeloma (MM), a blood cancer of plasma cells, is the third most common hematologic cancer in the United States,[1,2] with the median age of diagnosis of 69 years, and based on data from SEER during 2012 to 2018, the overall 5-year survival rate is 57.9%.[1] The treatment landscape of MM has evolved in recent years with the introduction of innovative targeted therapies and treatment options, such as high-dose chemotherapy with transplant, for those who are eligible. Across lines of therapy (LOTs) for MM, various combination therapies are used, which commonly include proteasome inhibitors, immunomodulatory drugs, or corticosteroids.[3] Within the past decade, a clinical trial program has reported that daratumumab (DARA), an anti-CD38 monoclonal antibody, further improves outcomes for patients with MM.[4] In fact, many treatment backbones for MM across LOTs now include DARA,[3] and DARA has gained approval as monotherapy and combination therapy for treatment of patients with relapsed or refractory MM and as combination therapy for newly diagnosed MM (NDMM).[5] To this end, patients initiating DARA may continue DARA use, even as other agents in the regimen and LOTs change. Duration of DARA treatment has been analyzed previously for each LOT[6,7]; however, there is a lack of information on the continuous use of DARA and its dosing frequency across multiple regimens or LOTs. This study examines the continuous duration of DARA treatment and the dosing frequency of DARA across multiple LOTs using real-world data from patients with MM in the United States.

METHODS

We performed a retrospective observational study using the Optum deidentified Clinformatics Data Mart database, consisting of Medicare and commercially insured patients with MM receiving DARA. Data were collected for patients with first observed treatment using DARA-containing regimens from November 1, 2015, to March 31, 2021. The index date was the date of initial DARA treatment observed with DARA-containing regimens. The baseline period included 6 months before the index date, and the follow-up period started from the index date until the date of DARA discontinuation for patients who discontinued DARA, or from the index date until the censored date for patients who did not discontinue DARA. The DARA discontinuation was defined as a gap of more than 60 days between 2 subsequent DARA claim dates (the discontinuation date was the date of the last DARA claim before the gap). When an event date (ie, DARA discontinuation) was not ascertained before the end of the follow-up, the censored date was either the end of continuous enrollment, date of hematopoietic stem cell transplant, date of clinical trial entry, or end of the study period, whichever came first. Eligible patients were aged 18 years or older, reported 1 or more medical or pharmacy claim for DARA, were diagnosed with MM before the index date (with 1 or more diagnosis code [ICD-9-CM: 203.0x or ICD-10-CM: C90.0x]), and reported continuous insurance coverage for 6 months or more before the index date. Patients were excluded for diagnoses of other types of malignancies, enrollment in a clinical trial, or diagnosis with amyloid light-chain amyloidosis, if such information was identified from the baseline period. Patients who received a transplant were excluded to focus the analysis on nontransplant patients initiating their first use of DARA therapy.

This analysis assessed the length of use of DARA, the probabilities for treatment discontinuation, and DARA dosing frequency. The duration of DARA use was defined as the time interval between first initiation and discontinuation, regardless of the treatment regimen or spanning multiple DARA-containing LOTs, as a time-to-event outcome using the Kaplan-Meier method. Dosing frequency was calculated as the average number of DARA doses during defined time periods. Dose adherence ratios were calculated as observed dosing frequency divided by the dosing frequency for US Food and Drug Administration-approved regimens (DARA and lenalidomide and dexamethasone [D-Rd] and DARA and pomalidomide and dexamethasone [D-Pd]). A subgroup analysis among patients with continuous insurance coverage for 12 months or more of follow-up after the index date was also conducted.

RESULTS

In total, 2124 patients initiating DARA therapy were included in this analysis. The baseline characteristics for all patients are shown in Table 1. The mean age was 70.9 years, with 40.0% aged 75 years or older. Most of the patients were White or Black (White, 64.8% and Black, 17.0%), approximately half were male (51.3%), and most presented with Medicare (75.8%), with the remaining proportion having commercial insurance (24.2%). Hypertension was reported in 67.6% of patients; calcium elevation, renal insufficiency, anemia, and bone abnormalities, also referred to as CRAB symptoms, were reported in 44.9%; diabetes occurred in 29.1%; and cardiovascular conditions and renal impairment occurred in 28.5% and 22.1% of patients, respectively. The median follow-up time was 14.2 months (interquartile range, 8.0-23.4) among all identified patients. The subgroup analysis of patients with 12 months or more of continuous insurance coverage included 1246 patients, and baseline characteristics for patients were similar compared with that of all patients (data not shown). In this group, the median follow-up time was 21.7 months (interquartile range, 16.1-30.4).

Among all patients, the median duration of continuous DARA use was 16.6 months (Figure, A), with 63.5% of patients remaining on DARA by 12 months and 33.1% by 24 months (Table 2). For patients with 12 months or more of continuous insurance coverage, the median length of DARA use was 24.7 months (Figure, B) and, by 12 and 24 months, 99.4% and 51.8% of patients remained on DARA treatment, respectively. The dose adherence ratios (observed DARA

TABLE 1. Baseline Characteristics of Patients With MM Initiating DARA-containing Treatment From the Optum Deidentified Clinformatics Data Mart Database from November 1, 2015, to March 31, 2021[a]

Characteristic	N=2124
Mean age ± SD (median), y	70.9±9.8 (72)
Age group, n (%)	
18-44 y	25 (1.2)
45-54 y	111 (5.2)
55-64 y	373 (17.6)
65-74 y	766 (36.1)
≥75 y	849 (40.0)
Male, n (%)	1090 (51.3)
Race, n (%)	
White	1377 (64.8)
Black	362 (17.0)
Asian	53 (2.5)
Hispanic	204 (9.6)
Unknown	128 (6.0)
Insurance type, n (%)	
Commercial	514 (24.2)
Medicare	1610 (75.8)
Index date year, n (%)[b]	
2016	130 (6.1)
2017	422 (19.9)
2018	443 (20.9)
2019	636 (29.9)
2020	493 (23.2)
Clinical characteristic, n (%)	
Hypertension	1435 (67.6)
CRAB symptoms	953 (44.9)
Diabetes	619 (29.1)
CV conditions	606 (28.5)
Renal impairment	470 (22.1)
Stroke/TIA	60 (2.8)
Peripheral neuropathy	11 (0.5)
Follow-up time, months	
Median (Q1-Q3)	14.2 (8.0-23.4)
Mean ± SD	17.1±12.3
Mean Quan-Charlson Comorbidity Index ± SD	3.1±3.2

[a]Abbreviations: CRAB, calcium elevation, renal insufficiency, anemia, and bone abnormalities; CV, cardiovascular; MM, multiple myeloma; Q1, First quartile; Q3, Third quartile; TIA, transient ischemic attack.
[b]Index date year refers to the date of first DARA treatment observed within DARA-containing regimens.

doses relative to the DARA doses per the label) were close to 1.0, particularly among patients with longer follow-up (Table 2).

DISCUSSION

This retrospective observational real-world study evaluated, for the first time, the continuous duration of DARA treatment and dosing frequency across multiple LOTs using data from US patients with MM. Nontransplant patients initiating their first use of DARA remained on therapy for a median of 16.6 months, with 63.5%, 33.1%, and 14.5% continuing DARA at 12, 24, and 36 months, respectively. Because this study used claims data, it is possible that patients were lost to follow-up owing to a change in insurance provider, or that the duration of therapy may have been limited by a loss of or inadequate insurance coverage, even if a patient was still on therapy at the end of the follow-up period. Hence, a subgroup analysis was conducted of patients with 12 months or more of continuous insurance coverage; among these patients with longer continuous coverage, the median duration of DARA use was longer at 24.7 months, with higher proportions continuing DARA therapy at 12 months (99.4%), 24 months (51.8%), and 36 months (22.8%). In addition, the mean dosing frequency of DARA in the real-world was similar to the dosing frequency on the approved label. These data demonstrate that adherence with the approved prescribing information is high, particularly among MM patients with longer DARA use.

Previous studies have evaluated real-world use of DARA in the United States and reported that the median duration of treatment across LOTs (with various combinations) was 9.8 months,[7] which is slightly longer compared with a median of 6.5 months reported by another group (with ranges from 4.1 to 8.8 months, depending on the LOT).[6] These studies do not follow DARA continuously. In our analysis, which included nontransplant patients initiating DARA use for the first time (ie, not necessarily frontline use), median treatment duration of DARA was relatively long (16.6 months). The real-world duration of therapy has also been evaluated in other MM regimens that do not include DARA. In particular, previous studies among nontransplant patients with NDMM found that real-world durations of therapy were estimated at a median of 5.5 months for bortezomib and

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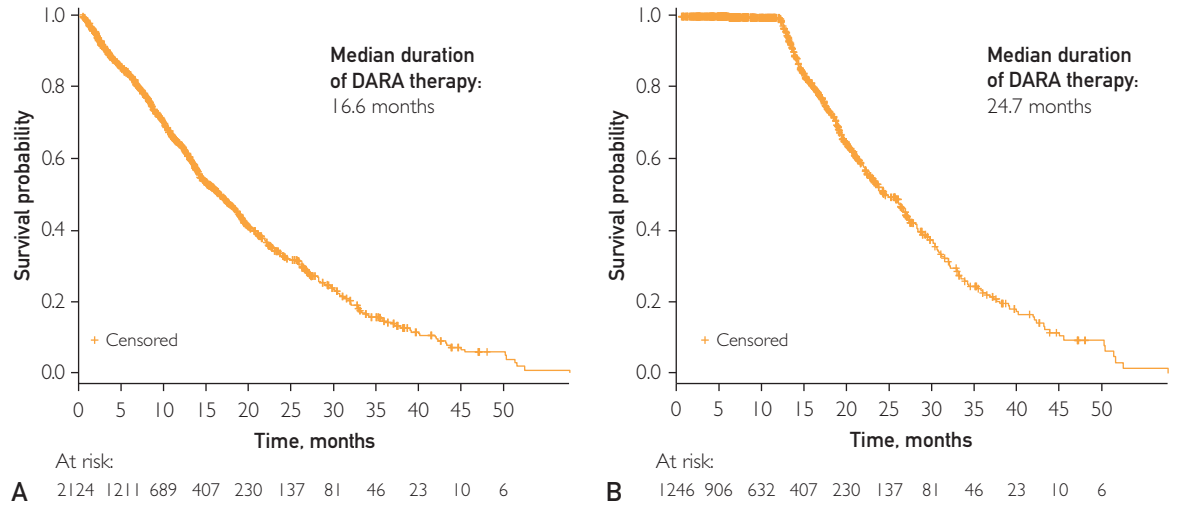

FIGURE. Duration of DARA treatment in (A) all patients and (B) patients with ≥12 months of continuous insurance coverage from the index date (DARA initiation date) to the treatment discontinuation of DARA regardless of the treatment regimen or the LOT number DARA is in (eg, 1st, 2nd). DARA, daratumumab; MM, multiple myeloma; LOT, line of therapy.

lenalidomide and dexamethasone (VRd),[8] 12.0 months for lenalidomide and dexamethasone (Rd), 5.9 months for bortezomib and dexamethasone (Vd),[9] and ~4 months for bortezomib-containing regimens.[10] Taken together, the real-world duration of therapy for DARA-containing regimens is generally longer compared with other MM therapies. When considering our results in the context of others, an important point is that we assessed DARA duration of therapy regardless of the LOT or treatment regimen, and it may have spanned multiple DARA-containing LOTs. It is likely that many patients who discontinued had relapsed or refractory MM that may have progressed. Furthermore, the use of DARA across LOTs changed during our study period; DARA was approved in 2015 for MM,[11] with approval in NDMM first occurring in 2018[12] and additional combination

TABLE 2. Percentage of Patients Remaining on DARA Treatment and Number of DARA Doses Over Time[a]

Time, month	Patients remaining on DARA treatment (N=2124) (%)	Observed DARA doses, mean ± SD	DARA doses per label[b]	Adherence ratio (observed DARA doses/DARA doses per label)[c]
3	90.5	9.6±2.4	11	0.87
6	83.2	15.0±3.1	17	0.88
9	72.6	18.5±3.4	20	0.92
12	63.5	22.0±3.8	23	0.96
18	46.5	28.8±4.6	30	0.96
24	33.1	35.4±6.0	36	0.98
36	14.5	48.1±8.6	49	0.98

[a]Abbreviations: DARA, daratumumab; D-Pd, daratumumab and pomalidomide/dexamethasone; D-Rd, daratumumab and lenalidomide/dexamethasone; FDA, US Food and Drug Administration.
[b]Dosing frequency was calculated as the average number of DARA doses during defined time periods.
[c]Dose adherence ratios were calculated as observed dosing frequency divided by the dosing frequency for FDA-approved regimens (D-Rd and D-Pd) provided in the prescribing information.

regimens for NDMM following in 2019.[13,14] Consequently, the study period in our analysis (2015-2021) invariably captured multiple LOTs spanning these approval dates, with dates after 2018 able to evaluate frontline DARA use. It is expected that as DARA continues to be used more in the frontline setting, the associated therapy durations may be longer, as is the case in several studies where patients received frontline therapy and were treated to progression.[15,16]

As discussed, the data from this real-world study reported a longer median duration of continuous DARA therapy compared with the other real-world analyses. However, this real-world duration of DARA use remains shorter than that observed in clinical trials. Across pivotal DARA phase 3 clinical trials like POLLUX, CASTOR, and APOLLO, the median duration of DARA treatment for patients with previously treated MM ranged from 11.5 to 24.5 months,[17-19] and an even longer therapy duration (47.5 months) was seen in the MAIA trial for transplant-ineligible patients with newly diagnosed MM.[20] The observed longer duration of therapy in clinical studies compared with the real-world can be attributed to the inherent differences between the clinical trial setting and real-world use, and availability of longer follow-up data commonly collected in clinical studies. In addition, as previously noted, the duration of therapy is expected to be longer for frontline use but, given the study period, we may have few first-line patients in our sample. However, comparisons between clinical trials and real-world analyses should be done with caution because rigorously controlled clinical trial settings are not replicated in the real-world.[21]

A subcutaneous formulation of DARA (DARA SC) was approved for use in 2020[22]; as such, DARA SC use could only be captured for part of our analysis after its approval. DARA SC has been associated with reduced administration and chair time[22,23] and higher patient satisfaction[24] compared with DARA by intravenous administration. Consequently, use of DARA SC may have a favorable effect on therapy duration and adherence, and the cost of DARA may be potentially reduced with longer use. Therefore, although our study reported that real-world DARA duration of therapy is relatively long, there remains a need for continued research to understand DARA use in the real-world.

In addition, we note an adherence ratio ranging from 0.87 at month 3 to 0.98 with a longer follow-up time. Improved adherence with longer follow-up may be due to the very favorable tolerance profile after patients become used to taking and tolerating the medication. Moreover, our data show high fidelity to the label, which indicates patients were not receiving more frequent dosing than expected. A recent analysis by Gordan et al[7] reported a higher DARA adherence ratio of 1.19; however, their analysis projected an adherence ratio for a 12-month period using data with a mean treatment duration of only 5.6 months (median, 9.8 months). The analysis did not consider patient attrition over time, possibly leading to an overestimate in adherence.[7] However, we show that duration of therapy for DARA-based regimens in the real-world is relatively long and adherence is high. Although our study was not designed to evaluate the effect of duration of therapy on efficacy, we interpret these results favorably, as it has been previously shown that continuous therapy and longer durations of treatment are associated with improved patient outcomes, including better tolerability and longer survival.[10,25-27]

Finally, there is a growing concern about treatment costs in MM. As this study has reported longer real-world duration of DARA and high adherence with the therapy, it is critical to understand its effect on the treatment cost. Hence, it is crucial to highlight that cost of DARA treatment reduces over time owing to less frequent dosing. In particular, frequency of dosing with DARA reduces from weekly dosing during the first 2 months to biweekly dosing during months 3 to 6, and then once-per-month dosing after 6 months of therapy. Calculations using the current wholesale acquisition cost per vial of DARA SC (DARA 1800 mg co-formulated with recombinant human hyaluronidase PH20 [rHuPH20; 2000 U/mL; ENHANZE drug delivery technology, Halozyme, Inc])[22] show that the cost of DARA decreases by 65% from the first 6 months ($155,016) to the second 6 months

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($54,712), and by 43% from the first year of treatment ($209,728) to the end of the second year of treatment ($118,542).[28] With longer, continuous use of DARA, the treatment cost in subsequent years is lower.

This study included a large sample of real-world MM patients across the United States and represented patients with a broad array of sociodemographic or social determinants and clinical factors, providing insight on patients with MM initiating DARA-containing regimens. Although claims data are extremely valuable for examining treatment patterns and other outcomes, claims are collected for the purpose of reimbursement and have some inherent limitations (eg, potential coding errors or omissions, misclassification of an outcome, such as the end of continuous eligibility because of death, etc). In addition, claims data sets often lack other information that would be potentially interesting to researchers, including data on reasons for therapy discontinuation and specific biologic information on risk stratification (standard vs high) in MM. Data are primarily from insured populations on Medicare Advantage plans among adults over 65 years of age, and results may not be generalizable to other populations. In addition, the follow-up period is not long enough to fully estimate the duration of DARA treatment in patients with NDMM. Furthermore, in the subgroup analysis, the potential for immortal time bias cannot be excluded. Future analyses are warranted to allow for a longer follow-up of DARA-based therapies, including a real-world evaluation of DARA SC.

In summary of this real-world study, over half of the patients with MM who received DARA-containing treatment remained on therapy for 16.6 months, and this was even longer among patients with continuous insurance coverage, indicating that the duration of DARA use is longer than previously observed among patients with MM in the United States. The DARA dosing frequency was consistent with that on the approved label.

POTENTIAL COMPETING INTERESTS

R.F. served as a consultant for AbbVie, Aduro, Amgen, Bayer, Bristol Myers Squibb, Celgene, GSK, Janssen, Juno, Kite Pharma, Merck, Novartis, ONCOtracker, Pharmacyclics, Sanofi, and Takeda; participated in scientific advisory boards for Adaptive Biotechnologies and ONCOtracker, Board of Directors Antegene. E.E.C., N.G-W., A.Z.F., & S.K. are employees of the Janssen Pharmaceutical Companies of Johnson & Johnson. All other authors declare no competing interests.

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Abbreviations and Acronyms: **DARA**, daratumumab; **DARA SC**, subcutaneous formulation of daratumumab; **LOT**, line of therapy; **MM**, multiple myeloma; **NDMM**, newly diagnosed multiple myeloma

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