

The Contribution of RWE to the Management of Relapsed/Refractory Multiple Myeloma

IN DETERMINING SAFETY AND EFFICACY, randomized controlled trials (RCTs) are considered the gold standard.¹ RCTs can evaluate cause and effect and minimize bias through their prospective design, randomization, pre-defined end points, and minimization of confounders.² However, it is difficult to determine potential benefits for those who were excluded from trials.¹

Real-world data (RWD) and real-world evidence (RWE) are other forms of evidence that complement RCT data. The FDA defines RWD as “the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.”³ These sources can include:

- Electronic medical records^{1,3-5}
- Administrative claims data^{1,3-5}
- Registries^{1,3-5}
- Hospital claims data¹
- Health surveys⁴
- Patient-reported outcomes⁴
- Wearable devices⁵
- Apps⁵

RWE is defined as “the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.” Just as there are different sources of RWD, different study designs or analyses can generate RWE. Examples can include pragmatic trials, large simple trials, and observational studies, which can be prospective or retrospective.³ In a retrospective observational study, investigators choose their study population and then use that population’s historical data that were collected prior to the start of the study. By contrast, in a prospective observational study, investigators collect data after they have identified their study population.⁶

End points of RWE studies may differ from those of RCTs and can include time to next treatment (TTNT), which can be used as a proxy for progression⁷⁻⁹; evaluation of real-world treatment patterns and outcomes⁷; health care resource utilization^{10,11}; and budget impact and cost-benefit models using total cost of treatment.^{7,12}

Value Provided by RWE Studies

RWE studies add value by complementing the data generated by RCTs.¹ Because RWE studies can utilize large sample sizes and cover longer time periods, they have the

potential to reveal adverse medication effects not detected in the initial trials.¹ For example, the FDA uses RWE to continue evaluating drug safety after approval.⁶

RWE studies are also more generalizable to the wider population, enhancing external validity.^{1,2} According to de Lusignan and colleagues, “Whilst RWD are inherently more messy, their advantage is that RWE studies will include people with multimorbidity, on usual prescribed doses, and standard patterns of adherence” as well as the “thresholds at which treatments are implemented.”¹

By including patient populations that may not have been studied prior to approval, RWE studies help stakeholders better understand the treatment’s risks and benefits under real-world conditions.^{1,6} In particular, these questions can be relevant to health care decision-makers.⁴ RWE represents the patient population that insurers are covering as well as the environment in which the patients are treated.⁴ Payers can use RWE to inform decision-making on multiple levels including formulary placement and determination of necessity.⁴

Limitations

Comparing care pathways, especially in medically complex patients, remains challenging.¹ RWE cannot confirm causality, though statistical methods can take confounders into account and control for bias; how to best minimize bias remains to be determined.^{1,5,6}

Because reducing bias shores up confidence in results, organizations have created and are creating guidelines and legislation for RWE study best practices.^{3,5,6} Orsini and colleagues note, “As the potential use of RWE to support decision-making for market authorization, reimbursement, and clinical guideline development grows, the need to trust that evidence grows correspondingly.”⁵ Among others, US lawmakers, the FDA, and a joint Special Task Force of the Professional Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE) have put forth guidance to optimize the use of RWE.

At the legislative level, The Food and Drug Administration Modernization Act of 1997 (FDAMA 114) and the 21st Century Cures Act (Cures Act) have provided relevant guidance. FDAMA 114 provided for communication about health care economic information not found in the product label.¹³ The Cures Act, which was signed into law in December 2016, clarifies language contained in FDAMA 114 and facilitates making medical advances

available to patients sooner. The Cures Act does this by laying the groundwork to determine the power of RWE (1) to facilitate the approval of additional indications for drugs that are already approved or (2) to fulfill or supplement required postapproval drug studies.^{6,14}

Within its RWE Program, the FDA has also developed a guiding framework. Among other things, the framework highlights how RWD can make clinical trials more efficient by⁶:

- Assembling geographically distributed research cohorts (eg, in drug development for rare diseases or targeted therapeutics)⁶
- Assessing trial feasibility by examining the impact of planned inclusion/exclusion criteria in the relevant population, both within a geographical area or at a particular trial site⁶
- Generating hypotheses for testing in randomized controlled trials⁶
- Identifying drug development tools (including biomarker identification)⁶
- Identifying prognostic indicators or patient baseline characteristics for enrichment or stratification⁶
- Informing prior probability distributions in Bayesian statistical models⁶

As part of its real-world evidence program, the FDA will also assess quality control to ensure that RWD/RWE and their uses meet the FDA's standards.⁶

The ISPOR/ISPE joint Special Task Force strives to improve the uptake of RWE by increasing the transparency of RWE studies so that they can be independently evaluated. To this end, the Special Task Force made the following recommendations on “good practices” in RWE studies: (1) Investigators should communicate at the beginning whether their study is to generate a hypothesis, or whether it already has a hypothesis that needs to be tested in a specific population; (2) before analyzing their data, investigators should publicly post, in a registry, their study protocol and how they plan to analyze the data; and (3) when publishing their results, investigators should provide an “attestation of conformance or deviation from the initial study protocol and analysis plan.”⁵ Following their issuance of “good practices,” the Special Task Force also joined with other stakeholders to identify ways to optimize RWE registration.⁵

Given the utility of RWD/RWE, it is instructive to see how RWD/RWE have been employed in the realm of multiple myeloma (MM). In their review, Terpos and colleagues highlight the gap between efficacy—“performance under ideal, controlled conditions” (ie, a clinical trial)—and

effectiveness or “performance of a regimen under real-world conditions.”¹⁵ They found that there are many potential reasons for this gap. For one, about 40% of patients with MM do not qualify for phase 3 clinical studies and are therefore unrepresented.¹⁵ Secondly, regimens have become more complex. They contain novel drugs and may be more toxic than previous regimens. Without RWD, it is difficult to know how feasible these regimens are and how adherent patients can be.¹⁵ Lastly, treatment goals change from patient to patient depending on patient-, treatment-, and disease-specific factors.¹⁵

To make data collection better, Terpos and colleagues suggest that stakeholders expand clinical trial eligibility criteria, collect real-world along with clinical trial data, standardize patient reported outcome data collection, and disseminate optimal treatment information from specialty treatment centers.¹⁵ By supplementing clinical trial data with RWD on efficacy and safety, quality of life, economic impact, satisfaction with treatment, and patient preference, treatment choices could be better informed.¹⁵

To capture what matters to patients in the real world, Terpos and colleagues identified symptom burden; adverse effects (AEs)/toxicities; quality of life including daily and physical activities; treatment cost (ie, the financial toxicity); level of convenience, including how treatment is administered (eg, oral treatment makes it easier to work, continue with daily activities); and comorbidities as factors of importance.¹⁵

Incorporating RWD may improve treatment effectiveness. For example, a patient may be more likely to persist on a more convenient, tolerable treatment that provides better quality of life.¹⁵ To improve comparisons of regimen effectiveness, more patient-related factors and endpoints need to be considered. To make comparisons using these RWD more valid, stakeholders also need to standardize how these data are compiled, reported, and analyzed.¹⁵

In another real-world study, Chari and team wanted to compare outcomes and treatment choices in patients with relapsed/refractory MM (RRMM) across 3 regimens. These RWD are needed because of the shortage of head-to-head studies for these regimens; many patients with MM are older (ie, the type of patient excluded from clinical trials), and older patients also tend to have comorbidities that increase their risk of negative outcomes.¹⁶

The 3 regimens included in the study were bortezomib plus lenalidomide/dexamethasone (VRd), carfilzomib plus lenalidomide/dexamethasone (KRd), and ixazomib plus lenalidomide/dexamethasone (IRd).¹⁶ To compare the regimens, the investigators used TTNT, a surrogate for progression-free survival (PFS); frailty, which can be prognostic in patients with MM; and TTNT by frailty. They also examined how patient-, disease-, and treatment- related factors affected treatment choice.¹⁶

They found that, in line of therapy (LOT) 2 or later, the risk of regimen discontinuation was significantly lower for those treated with IRd than KRd (HR, 0.71; $P = .0209$).¹⁶ The risk of discontinuation was also lower compared with regimens containing bortezomib (HR, 0.85).¹⁶ They also found, in LOT 2 or later, the risk of discontinuing part of the regimen (the proteasome inhibitor [PI] or lenalidomide) was lower for regimens containing ixazomib. For IRd versus KRd, the HR was 0.65 for discontinuing the PI ($P = .0034$) and 0.64 for discontinuing lenalidomide ($P = .0015$).¹⁶ For IRd versus VRd, the HR was 0.62 for discontinuing the PI ($P = .0003$) and 0.75 for discontinuing lenalidomide ($P = .0312$).¹⁶ For KRd versus VRd, however, the risk was comparable; the HR was 0.94 for discontinuing the PI and 1.18 for discontinuing lenalidomide ($P > .05$ for both).¹⁶ TTNT was comparable between the 3 regimens in LOT 2 or later.¹⁶

In subgroup analyses of patients with a modified frailty score of intermediate to frail, the risk of death or starting another LOT was also lower in those treated with IRd versus KRd (HR, 0.70; $P = .0389$).⁶ In those treated with KRd versus VRd, however, the risk was higher (HR, 1.38; $P = .0481$).¹⁶ There was not a significant difference in this population between those treated with IRd or VRd.¹⁶ However, there was a significantly higher risk in the IRd versus KRd group (HR, 0.70; $P = .0389$) and the KRd versus VRd group (HR, 1.38; $P = .0481$).¹⁶ No adjusted TTNT differences were seen among fit patients.¹⁶

For regimen choice, high cytogenetic risk and prior immunomodulator (IMiD) exposure were independently associated with a significantly increased likelihood of treatment with IRd over VRd ($P < .02$).¹⁶ Symptomatic relapse, relapse after transplant, prior PI exposure, and being refractory to last prior therapy were significantly associated with choosing KRd over IRd; prior IMiD exposure, however, was independently associated with a significantly increased chance of treatment with IRd over KRd ($P < .02$).¹⁶ For KRd versus VRd, high-risk cytogenetics, symptomatic relapse, peripheral neuropathy, prior transplant history, prior PI exposure, and prior IMiD exposure were all significantly associated with an increased likelihood of treatment with KRd over VRd ($P < .04$).¹⁶

The investigators concluded that these results suggest that effectiveness is not as high in the real world as it is in clinical trials, which may be due to the number of patients who do not meet the trial eligibility criteria. They also suggest that tailoring treatment to the individual patient and taking things such as frailty into consideration could improve outcomes, especially considering the number of elderly patients with RRMM.¹⁶

Like Chari and team, Davies et al also compared triplets, including not only those containing PIs but also those containing daratumumab. Bortezomib has been the

traditional backbone for triplets used to treat RRMM. However, since bortezomib's approval in 2003, the PI carfilzomib was approved in 2012, and the PI ixazomib and the monoclonal antibody daratumumab were both approved in 2015, shifting the treatment landscape.¹⁷⁻²¹

To compare the effectiveness of bortezomib, carfilzomib, daratumumab, and ixazomib when incorporated into triplets used to treat patients with RRMM, Davies and colleagues completed a retrospective cohort study using data from 2007 to 2018 from Optum's deidentified electronic health records database.²¹ The database includes 6500 clinics in 50 states and is expected to reflect the general population.²¹ Qualified patients were adults with a MM diagnosis who had been treated with at least 1 LOT and then began a triplet regimen containing bortezomib, carfilzomib, daratumumab, or ixazomib combined with either an Rd or pomalidomide plus dexamethasone backbone on or after January 1, 2014.²¹ The primary outcome was TTNT (time from the start of the index regimen to initiation of subsequent LOT or death, whichever occurred first), a surrogate for PFS in real-world studies.²¹ The index regimen's duration of therapy, the time from initiation of the index regimen to discontinuation of the last drug in the regimen plus a run-out period, was an additional outcome evaluated.²¹ Patient-LOT was the unit of measure; the first date that each triplet regimen was initiated in LOT 2 or later was the index date for each triplet LOT of interest.²¹

In the stratified analysis for LOT 2 or later, median TTNT was also stratified by regimen with triplets containing ixazomib having the longest TTNT (11.1 months), followed by those containing bortezomib (9.8 months), daratumumab (7.2 months), and carfilzomib (6.7 months).²¹ Compared with regimens containing bortezomib (reference), the risk of next treatment initiation or death was also significantly lower with regimens containing ixazomib (HR, 0.80; $P = .0299$); it trended toward being significantly higher with carfilzomib regimens compared with bortezomib regimens (HR, 1.15; $P = .0529$). There was not a significant difference between daratumumab- and bortezomib-based regimens (HR, 1.04; $P = .6567$).²¹

However, on adjusted analyses for LOT 2 or later, there was no significant difference between regimens for risk of next treatment initiation or death compared with bortezomib-based regimens.²¹

When looking just at triplets using a lenalidomide/dexamethasone backbone or a pomalidomide/dexamethasone backbone, investigators found that the risk of next treatment initiation or death was significantly higher with carfilzomib plus lenalidomide/dexamethasone compared with bortezomib plus lenalidomide/dexamethasone (reference).²¹ However, in adjusted analyses, there was no significant difference.²¹ When evaluating a pomalidomide backbone, no significant differences were seen.²¹

The authors concluded that median TTNT was longest for triplets containing ixazomib compared with those containing bortezomib, daratumumab, or carfilzomib. However, on adjusted analyses, no significant difference was seen between any of the triplets for risk of next treatment initiation or death at LOT 2 or later. No significant difference was found either on the exploratory analysis of regimens with a lenalidomide/dexamethasone or pomalidomide/dexamethasone backbone. The investigators suggest more research is needed to improve understanding of differences between clinical data and real-world results.²¹

Because little is known about the cost of triplet regimens because of their relatively recent approval, Hollman and colleagues analyzed the real-world cost of 5 triplet regimens used to treat RRMM.²² The investigators realized that stakeholders including professional groups such as the American Society of Clinical Oncology and pharmacy benefit managers can use these data to assess the value of an intervention. As health care costs rise, this type of information can be used to keep cost in mind while still optimizing patient outcomes.

In their 1-year cost analysis, they estimated duration of treatment using PFS and evaluated 5 National Comprehensive Cancer Network–recommended and FDA-approved regimens²²:

1. Daratumumab plus lenalidomide plus dexamethasone (DARA/LEN/DEX)
2. Daratumumab plus bortezomib plus dexamethasone (DARA/BOR/DEX)
3. Elotuzumab plus lenalidomide plus dexamethasone (ELO/LEN/DEX)
4. Carfilzomib plus lenalidomide plus dexamethasone (CAR/LEN/DEX)
5. Ixazomib plus lenalidomide plus dexamethasone (IXA/LEN/DEX)

To evaluate cost, they analyzed administration costs, costs associated with AEs, comedICATIONS and 1-time costs, drug acquisition costs, monitoring costs, and subsequent therapy costs.²²

Finally, to estimate costs, the investigators used the RED BOOK for wholesale acquisition cost²²; the RED BOOK and Ollendorf and colleagues' report to determine subsequent costs²²; the Centers for Medicare & Medicaid Services 2018 Physician Fee Schedule to determine the cost of administration²²; the Centers for Medicare & Medicaid Services nonfacility national payments to determine the cost of monitoring and the cost of comedICATIONS²²; and Roy and colleagues' RRMM cost analysis along with AE rates included in the prescribing information for each triplet to determine the cost of managing AEs.²²

The investigators found that the greatest contributors to cost were the acquisition of the drug and treatment length.²² From least to most expensive, the base case average monthly cost per patient by triplet was²²:

1. DARA/BOR/DEX: \$13,890
2. IXA/LEN/DEX: \$22,231
3. ELO/LEN/DEX: \$24,322
4. DARA/LEN/DEX: \$26,410
5. CAR/LEN/DEX: \$27,432

They concluded that the lowest cost per patient for 1 year of treatment appeared to be DARA/BOR/DEX, whereas CAR/LEN/DEX appeared to be the most expensive. They also cautioned that the data were modeled; therefore, data on real-world treatment patterns would improve our understanding of the cost of triplet therapy. Nevertheless, the current study is informative for health care stakeholders.²²

To continue adding to the data on recently approved MM treatments, Bruno and colleagues retrospectively evaluated data from over 350 community oncology providers in a longitudinal, 2-phase study to evaluate real-world treatment patterns and outcomes in patients with RRMM treated with at least 2 lines of therapy.²³ The objectives were to describe treatment regimens and sequence, describe therapy lines, assess AEs, and evaluate outcomes through median real-world PFS (rwPFS) and median real-world overall survival (rwOS) across lines of therapy and by “older” versus “newer” treatments.²³ The investigators presented the data descriptively without statistical analyses.²³

The authors reported the following results. For first-line treatment, patients most commonly received bortezomib (n=357 of 456, 78.3%) and lenalidomide (n=278 of 456, 61.0%).²³ From first- to fourth-line treatment, median rwPFS decreased from 12.0 months to 2.9 months, and median rwOS decreased from 48.2 months to 7.8 months.²³ When outcomes were stratified by newer (bortezomib, carfilzomib, daratumumab, elotuzumab, ixazomib, lenalidomide, panobinostat, and pomalidomide) versus older agents, investigators found that newer agents had numerically higher rwPFS in first- and second-line usage, although 95% CIs overlapped.²³ Newer agents also had numerically higher rwOS across all lines, but again, 95% CIs overlapped.²³ Although lenalidomide and bortezomib were the clear choices in earlier lines of therapy, by the third-line setting, no therapy dominated, likely because of a lack of defined treatment pathways.²³

Bruno and colleagues concluded that clinical benefit seems to lessen with time, seeing as how TTNT and therapy duration usually decreased with more lines of treatment.²³

In the real world, the number of patients relapsing is probably higher than what has been seen in clinical trials, underscoring the need for more treatment choices.²³ Newer agents may be better than older agents at increasing rwPFS and rwOS especially as part of earlier treatment lines, but more research is needed.²³ The authors conclude that this study highlights the importance of incorporating new treatments early into treatment regimens in the real-world setting so a wide range of patients can benefit from their use.²³

To ensure the best outcomes for patients with RRMM, RWD and RWE studies are needed to complement clinical trial data.

Braunlin and colleagues also used recent RWD to evaluate MM trends and outcomes given all the new MM treatments and regimens.²⁴ They conducted a retrospective cohort study using data on patients with MM from Flatiron Health electronic health records from 2011 to 2019.²⁴ The primary research objectives were to describe patients' demographics and clinical qualities as well as how MM treatments/regimens varied by LOT and year.²⁴

They found that, in 10,553 patients, the use of doublets—either an IMiD plus dexamethasone or a PI plus dexamethasone—decreased, whereas the use of a triplet—a PI plus an IMiD plus dexamethasone—increased.²⁴ By 2018-2019, across all lines of treatment, triplets replaced doublets as the most frequently prescribed regimen: first line = 61.6%, second line = 44.1%, third line = 41.6%, fourth line = 41.7%, and fifth line or later = 34.0%. The most dramatic decrease in the use of doublets was in the front-line setting, where their use dropped by almost half by the study's end.²⁴ Not surprisingly, the investigators also found that the use of triplets specifically containing monoclonal antibodies increased following their 2015 approval.²⁴

According to the authors, “approval of these new agents increased the number of treatment options and paved the way for more complex drug class combinations. However, even with these new therapies and combination regimens, patients continue to relapse and additional efficacious and safe therapies are needed in this highly complex patient population.”²⁴

To ensure the best outcomes for patients with RRMM, RWD and RWE studies are needed to complement clinical trial data. Up to 40% of patients with myeloma do not qualify for phase 3 trials; therefore, how to best treat these patients remains to be seen.¹⁵ RWE studies include patients unrepresented in clinical trials under real-world treatment conditions, and they bring gaps between trial and real-world results into focus.^{1,15} This knowledge can then be used to optimize MM treatment going forward. ♦

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