Original Study

Generic Lenalidomide Rivelime Versus Brand-name Revlimid® in the Treatment of Relapsed/Refractory Multiple Myeloma: A Retrospective Single-center Experience on Efficacy, Safety and Survival Outcome

Meral Beksac, Guldane Cengiz Seval, Derya Koyun, Pervin Topcuoglu, Meltem-Kurt Yuksel, Gunhan Gurman, Osman Ilhan

Abstract

In this retrospective observational study, relapsed/refractory multiple myeloma patients receiving singlet, doublet (Rd) or triplet (Rd plus carfilzomib, ixazomib or bortezomib) lenalidomide containing regimens were evaluated in terms of efficacy, safety and survival outcome with original brand-name lenalidomide (Revlimid®) vs. generic equivalent (Rivelime®). Our findings revealed similar efficacy and safety profile and similar survival outcome between original and generic lenalidomide.

Background: This study aimed to compare use of original brand-name lenalidomide (Revlimid®) vs. generic equivalent (Rivelime®) in terms of efficacy, safety and survival outcome in patients with relapsed/refractory multiple myeloma (RRMM) **Patients and Methods:** A total of 184 patients RRMM (median age: 62 years, 60.9% were males) who received singlet, doublet or triplet lenalidomide-containing regimens including either Revlimid® (n=74) or Rivelime® (n=110) were included in this study. Treatment response was based on evaluation of objective response to treatment (ORR) including the sum of patients who achieved partial response (PR), very good partial responses (VGPR) or complete response (CR) to therapy. Progression-free survival (PFS), overall survival (OS) and safety data were also recorded. **Results:** Revlimid® and Rivelime® groups were similar in terms of ORR (54.1 vs. 60.0%), CR (22.5 vs. 28.8%), VGPR (55.0 vs. 50.0%) and PR (22.5 vs. 21.2%) rates. Median (SE) PFS time were similar between Rivelime® vs. Revlimid® treated patients who were in the 2nd line (30.3(3.8) vs. 22.7(7.0) months, p=0.827) or 3rd line of therapy (38.1(12.1) vs. 20.1(0.9) months, p=0.147) at lenalidomide initiation. Two groups also had similar OS rate (83.8 vs. 73.6%) and OS time (mean 122.3 vs. 123.5 months). Side effects were manageable in both groups. **Conclusion:** In conclusion, replacing Revlimid® with its generic version Rivelime® in singlet, doublet or triplet lenalidomide containing RRMM regimens seems not to compromise the efficacy of treatment, and to yield a similarly improved response rates and survival outcome and no additional toxic effects, enabling a long-term therapy.

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Keywords: Multiple myeloma, Relapsed/refractory setting, Lenalidomide, Brand-name, Generic equivalent, Oncological outcome

Abbreviations: AEs, Adverse events; ASCT, Autologous stem cell transplantation; CR, Complete response; IMiDs, Immunomodulatory drugs; IRd, Ixazomib-lenalidomide-dexamethasone; ISS, International Staging System; KRd, Carfilzomib-lenalidomide-dexamethasone; ORR, Objective response to treatment; OS, Overall survival; PFS, Progression-free survival; PIs, Proteasome inhibitors; PR, partial response; Rd, Lenalidomide-dexamethasone; RRMM, Relapsed/refractory multiple myeloma, VGPR, Very good partial responses; VRd, Bortezomib-lenalidomide-dexamethasone; VTE, Venous thromboembolism.

Department of Hematology, Ankara University School of Medicine, Ankara, Turkey

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Address for correspondence: Prof. Meral Beksac, M.D., Ankara University,Cebeci Hospital, Department of Hematology, Dikimevi, 06620 Ankara, Turkey.
E-mail contact: beksac@medicine.ankara.edu.tr

Introduction

Multiple myeloma (MM) is a plasma cell neoplasm representing the second most common hematological malignancy.[1] Although introduction of modern therapies over the last decades, such as proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) enabled an improved survival and a prolonged disease control in MM patients, the prognosis still remains to be poor in those with relapsed /refractory disease.[1-3]

Lenalidomide, a tumoricidal IMiD with anti-proliferative, pro-apoptotic and anti-angiogenic effects on plasma cells, has been

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widely used in the management of MM based on its efficacy reported in newly diagnosed transplant-eligible and transplant-ineligible patients, in patients with relapsed/refractory MM (RRMM) as well as in the post-transplant maintenance setting.[3-7]

Although the brand-name lenalidomide (Revlimid) has been used in the clinical trials with MM patients in various settings, it is considered one of the most expensive original drugs in the market.

In Turkey, Rivelime has been approved as a generic equivalent of Revlimid since 2017 and both original and generic forms of the drug can be used in the first- line setting as well as in the subsequent lines of therapy in the management of MM.

However, apart from one study on the efficacy and adverse events (AEs) with use of original versus generic lenalidomide for doublet therapy in RRMM patients,[6] no studies to date investigated the comparative efficacy, safety and survival outcome with use of original versus generic lenalidomide containing regimens in RRMM patients.

Therefore, this retrospective single-center study aimed to compare the use of original brand-name lenalidomide (Revlimid) versus generic equivalent (Rivelime) in terms of efficacy, safety and survival outcome in patients with RRMM receiving singlet, doublet or triplet lenalidomide-containing regimens.

Patients and Methods

Study Population

A total of 184 patients with RRMM (median age: 62 years, range, 35-92 years, 60.9% were males) who received singlet, doublet or triplet lenalidomide-containing regimens including either Revlimid (n=74) or Rivelime® (n = 110) were included in this retrospective observational study conducted at a tertiary care hematology clinic from June 2004 to October 2020. Inclusion criteria were ≥18 years of age, diagnosis of multiple myeloma and disease progression in accordance with the criteria defined by International Multiple Myeloma Working Group, presence of a relapse after a single agent or in combination with proteasome inhibitors, current initiation of a lenalidomide containing treatment regimen (singlet, doublet or triplet) and availability of data on treatment response assessment.

This study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee (Date of Approval: 03.06.2020; Protocol No: İ5-299-20).

Data Collection

Data on patient demographics (age, gender), disease characteristics (M protein type, International Staging System [ISS] scores and FISH findings) and treatment characteristics including autologous stem cell transplantation (ASCT), prior lines of therapy and current lenalidomide containing regimens (singlet, doublet, and triplet) were recorded at baseline. Treatment response was based on the evaluation of objective response to treatment (ORR) including the sum of patients who achieved partial response (PR), very good partial responses (VGPR) or complete response (CR) to therapy. Duration of follow up, progression-free survival (PFS, rate and time), overall survival (OS, rate, and time) and safety data (AEs, treatment discontinuation, grade ≥3 hematologic toxicity, any grade non-hematologic toxicity, treatment discontinuation, dose changes) were also recorded.

Statistical Analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). Descriptive statistics were used to summarize the baseline characteristics. Survival analysis was made via Kaplan Meier analysis and comparisons were made via Log-Rank test. Data were expressed as mean (standard error [SE]), median (minimum-maximum), 95% confidence interval (CI) and percent (%) where appropriate.

Results

Baseline Characteristics

Overall, median age was 62 years (range, 35-92 years) and males composed 60.9% (n = 112) of study population. The lenalidomide was Revlimid in 74 (40.2%) patients and Rivelime in 110 (59.8%) patients. Overall, 51(27.7%) patients received the singlet lenalidomide therapy, 80(43.5%) patients received doublet therapy with lenalidomide-dexamethasone (Rd), and 53(28.8%) patients received lenalidomide-containing triplet therapy (Rd plus carfilzomib, ixazomib or bortezomib). The triplet regimens included bortezomib-lenalidomide-dexamethasone (VRd) in 30(16.3%), carfilzomib-lenalidomide-dexamethasone (KRd) in 19(10.3%), and ixazomib-lenalidomide-dexamethasone (IRd) in 4(2.2%) patients.

No significant difference was noted between Revlimid and Rivelime groups in terms of baseline characteristics including patient demographics, ASCT (71.6 and 72.7%), M protein type (IgG Kappa in 41.9% and 39.1%, respectively), ISS score (median 2.0 in each group) and FISH findings (normal in 81.1 and 76.4% of patients, respectively) (Table 1).

In both Revlimid and Rivelime groups, the treatment was based on singlet regimen (32.4 and 24.5%, respectively) or lenalidomide-dexamethasone combination (Rd) therapy (41.9 and 44.5%, respectively) in most of patients. Most of patients were on the second line (54.1 and 44.5%, respectively) or third line (20.3 and 14.5%, respectively) of therapy at the initiation of lenalidomide treatment, in both groups. No significant difference was noted between the study groups in terms of treatment characteristics (Table 1).

Treatment Response

Overall, 40(54.1%) patients in Revlimid group and 66(66.0%) patients in Rivelime group achieved an objective response to therapy. Of the 106 responders, 28 (24.1%) patients achieved a CR, 55 (47.4%) patients achieved a VGPR, and 23(19.8%) patients achieved a PR as their best response to treatment. ORR (54.1 vs. 60.0%), CR (22.5 vs. 28.8%), VGPR (55.0 vs. 50.0%), and PR (22.5 vs. 21.2%) rates were similar between Revlimid versus Rivelime groups (Table 2).

No significant difference was noted in treatment response with respect to prior lines of therapy (Table 2).

Survival Outcome

PFS rate and median (SE) PFS time were similar between Rivelime versus Revlimid treated patients who were in the second line (37.7 vs. 55.0% and 30.3(3.8, 95% CI: 22.0-37.7) vs. 22.7(7.0,

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Table 1 Baseline demographic, clinical and treatment-related characteristics

		Revlimid® (n=74)	Rivelime® (n=110)	p value
Age (years) median (range)		63 (35-92)	60 (35-88)	0.801
Gender (Male/Female)		44/30	68/42	0.748
ASCT, n(%)		53 (71.6)	80 (72.7)	0.869
M protein type (serum), n(%)				
IgG kappa		31 (41.9)	43 (39.1)	0.312
IgG lambda		7 (9.5)	11 (10.0)	
IgA kappa		4 (5.4)	14 (12.7)	
IgA lambda		6 (8.1)	10 (9.1)	
Light chain		12 (16.2)	11 (10.0)	
ISS at the time of diagnosis, median (range)		2 (1-3)	2 (1-3)	0.800
Stage I, n(%)		15 (20.3)	20 (18.2)	
Stage II, n(%)		31 (41.9)	43 (39.1)	
Stage III, n(%)		28 (37.8)	47 (42.7)	
FISH findings, n(%)				
Normal		60 (81.1)	84 (76.4)	0.447
17p deletion		6 (8.1)	8 (7.3)	0.367
13q deletion		11 (14.9)	19 (17.3)	0.665
t(4;14)		2 (2.7)	2 (1.8)	0.687
t(11;14)		4 (5.4)	5 (4.5)	0.791
Lenalidomide containing regimens, n(%)				
Singlet		24 (32.4)	27 (24.5)	0.372
Doublet (Rd)		31 (41.9)	49 (44.5)	
Triplet	KRd	6 (8.1)	13 (11.8)	
	IRd	3 (4.1)	1 (0.9)	
	VRd	10 (13.5)	20 (18.2)	
Line of therapy at lenalidomide initiation				
2nd line		40 (54.1)	49 (44.5)	0.310
3rd line		15 (20.3)	16 (14.5)	
≥4th lines		2 (2.7)	10 (9.1)	
Maintenance		17 (23.0)	35 (31.8)	

ASCT: Autologous stem cell transplantation; ISS: The International Staging System; Rd: Lenalidomide-dexamethasone; KRd: carfilzomib-lenalidomide-dexamethasone; IRd: Ixazomib-lenalidomide-dexamethasone; VRd: bortezomib-lenalidomide-dexamethasone

95% CI: 8.9-36.4) months, respectively, $P = .827$) or third line of therapy (37.5 vs. 20.0% and 38.1(12.1, 95% CI: 14.4-61.9) vs. 20.1(0.9, 95% CI: 18.2-22.0) months, respectively, $P = .147$) at lenalidomide initiation (Table 3, Figure 1)

After median 41.9 months and 47.6 months of follow up, respectively, the survived patients composed 83.8% (62/74) and 73.6% (81/110) of Revlimid and Rivelime groups, with no significant difference between treatment groups in terms of duration of follow up ($P = .060$) and survival rates ($P = .105$) (Table 4).

Mean (SE) OS time was 123.3(14.2, 95% CI: 95.4-151.2) months in the overall study population, and was similar between Revlimid (122.3(8.9, 95% CI:104.8-139.8) months) and Rivelime (123.5(11.5,95% CI: 100.8-146.1) months) groups (Long rank P value: .484) (Table 4, Figure 2).

Safety Data

No significant difference was noted between Revlimid and Rivelime groups in terms of safety data. AEs were manageable in both Revlimid and Rivelime groups with similar rates of any grade nonhematologic toxicities, including fatigue (51.4 vs. 52.8%), diarrhea (36.5 vs. 37.2%), muscle weakness (33.8 vs. 32.7%), rash (35.1 vs. 39.1%) and peripheral neuropathy (18.9 vs. 20.9%) in most patients. A significantly higher rate of grade ≥3 hematologic toxicity was noted in the Revlimid group than in the Rivelime group (25.7 vs. 13.6%, $P = .021$), while this AE-related difference between groups disappeared on analysis adjusted for the line of therapy (Table 5).

Two patients (2.7%) in Revlimid group and 7 patients (6.4%) in Rivelime group developed venous thromboembolism (VTE) (grade 4 toxicity) but recovered with therapy; no other patient developed VTE. Pneumonitis was the most common infection in both groups and (32.4 vs. 30.0%, $P = .35$). Treatment discontinuation due toxicity was noted in 55 patients (Revlimid/ Rivelime: 23/32), and the most common adverse event responsible for discontinuation was myelosuppression in both groups (Revlimid/ Rivelime:19/22) (Table 5).

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Table 2 Treatment Response Overall and According to Lines of Therapy

	Overall			According to the line of therapy at lenalidomide initiation										*P* Value
				Second line of therapy			Third line of therapy			≥Fourth line of therapy				
	Rivelime	Revlimid	*P* Value	Total	Rivelime	Revlimid	Total	Rivelime	Revlimid	Total	Rivelime	Revlimid		
Treatment response[a]														
ORR (n = 148)	66(60.0)	40(54.1)	0.131	78(62.9)	46(59.0)	32(41.0)	20(16.1)	10(50.0)	10(50.0)	8(6.5)	8(100.0)	0(0.0)		<0.001
CR (n = 43)	19(28.8)	9(22.5)	0.381	19(44.2)	11(36.7)	8(61.5)	7(16.3)	6(20.0)	1(7.7)	2(4.7)	2(6.7)	0(0.0)		0.381
PR (n=29)	14(21.2)	9(22.5)	0.373	15(51.7)	8(50.0)	7(53.8)	6(20.7)	2(12.5)	4(30.8)	2(6.9)	2(12.5)	0(0.0)		0.373
VGPR (n = 76)	33(50.0)	22(55.0)	0.131	44(57.9)	27(58.7)	17(56.7)	7(9.2)	2(4.3)	5(16.7)	4(5.3)	4(8.7)	0(0.0)		0.131
PD (n = 24)	9(8.2)	9(12.2)	0.859	7(29.2)	3(23.1)	4(36.4)	9(37.5)	5(38.5)	4(36.4)	2(8.3)	1(7.7)	1(9.1)		0.859
Total (n = 172)	75(60.5)	49(39.5)	-	85(49.4)	49(46.7)	36(53.7)	29(16.9)	15(14.3)	14(20.9)	10(5.8)	9(8.6)	1(1.5)		0.131

[a] Forty-eight patients (42 in ORR, 15 in CR, 6 in PR, 21 in VGPR and 6 in PD groups) were on maintenance therapy.

Discussion

Our findings in RRMM patients who received singlet, doublet (Rd) or triplet (Rd plus carfilzomib, ixazomib or bortezomib) lenalidomide-containing regimens revealed no significant difference between original (Revlimid) and generic (Rivelime) lenalidomide in terms of ORR (54.1 vs. 66.0%), CR (22.5 vs. 28.8%), VGPR (55.0 vs. 50.0%) and PR (22.5 vs. 21.2%), as well as the OS rate (83.8 vs. 73.6%) and OS time (mean 122.3 and 123.5 months). The Revlimid and Rivelime groups were also similar in terms of baseline patient and tumor characteristics, treatment approach (second-third line in most of patients, as a monotherapy in nearly one third of patients, as Rd in nearly half of patients) and duration of follow up (41.9 vs. 47.6 months). Side effects were manageable and nonhematologic toxicity profile (fatigue, diarrhea, muscle weakness, rash and peripheral neuropathy in most cases) was similar between treatment groups, while Revlimid versus Rivelime was associated with the higher likelihood of grade ≥3 hematologic toxicity (25.7% and 13.6%, respectively).

Likewise, in a past study with 98 RRMM patients on lenalidomide-dexamethasone combination (Rd) regimens in Turkey, the authors reported no significant difference between original lenalidomide (n = 55) and generic lenalidomide (n = 43) groups in terms of overall response rate (67.2% and 60.4%, respectively) and CR (14.5% and 20.9%), whereas a higher VGPR rate (45.4% and 18.6%) was noted with the use of original versus generic form of the drug.[6]

The current study showed that the generic and original forms of lenalidomide have similar efficacy in the treatment of RRMM, when used as a singlet regimen, doublet therapy (Rd) or triplet therapy (Rd plus carfilzomib, ixazomib or bortezomib). These findings seem consistent with data from clinical trials on the favorable efficacy of lenalidomide in RRMM patients, including MM-009 trial (overall response rate: 61%, median OS: 29.6 months),[8] MM-010 trial (overall response rate: 60.2%, median progression-free survival [PFS]: 4 months)[9] and MM-021 trial (disease control rate: 94.7%, overall response rate: 47.6%, median PFS: 8.3 months).[10]

Use of Rd combination (lenalidomide–dexamethasone) in MM patients was also reported to be associated with an overall response rate of 68% to 91% in the newly diagnosed setting[4,11,12] and to have a significant PFS benefit in the post-transplant maintenance setting.[13-15] The studies with Rd combination (lenalidomide–dexamethasone) forming the backbone of therapy such as ASPIRE, POLLUX, TOURMALINE and ELOQUENT revealed that triplet regimens were more efficacious than doublet regimens in RRMM with overall response rates of 78.0% to 92.9%, PFS rate of 68.0% to 83.2% and OS rate of 73.3%.[16-19]

The response rates (%), PFS (months) and 24-month OS (%) achieved with the triplet (Rd plus inclusion of a novel agent) versus doublet (Rd only) regimens were reported to be 87.0% versus 67.0 %, 26.3 months versus 17.6 months, and 73.0% versus 65.0%, respectively for carfilzomib[16] and to be 78% versus 72%, 20.6 months versus 14.7 months, and not reached, respectively for ixazomib.[18]

In the TOURMALINE trial with 722 RRMM patients who received ixazomib plus Rd (ixazomib group) or placebo plus Rd,

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Figure 1 Kaplan Meier analysis for progression-free survival (PFS) with respect to lines of therapy in relapsed/refractory multiple myeloma patients treated with brand-name lenalidomide (Revlimid) versus generic equivalent (Rivelime).

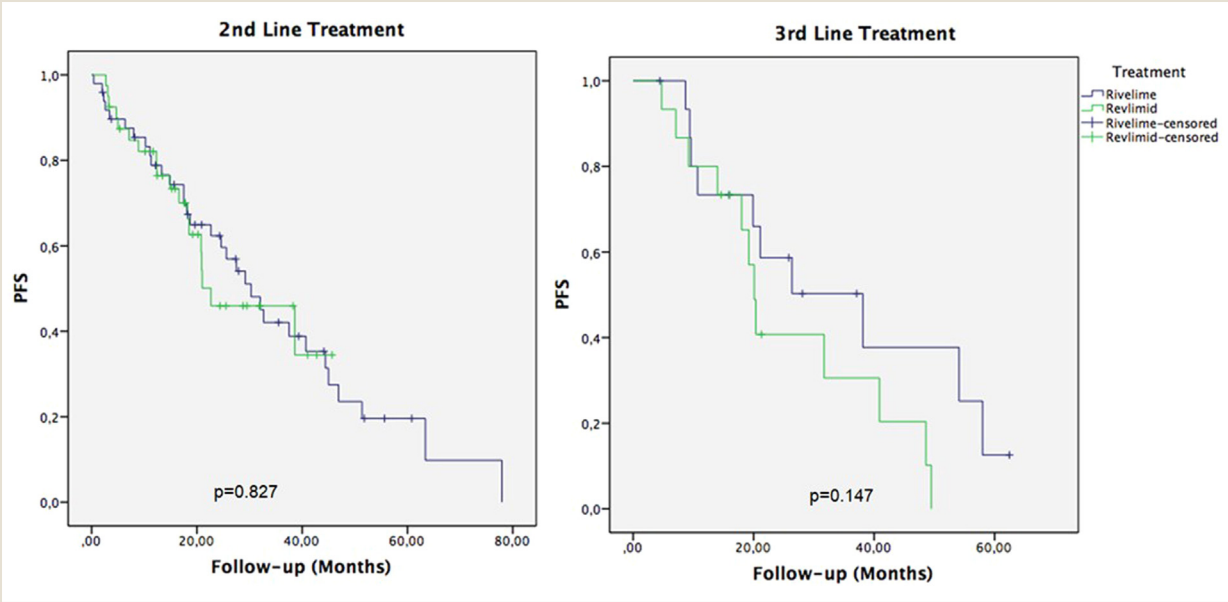


Table 3 Progression-free Survival According to Line of Therapy

	Line of Therapy at Lenalidomide Initiation					
	Second line of therapy			Third line of therapy		
Survival outcome	**Total**	**Rivelime**	**Revlimid**	**Total**	**Rivelime**	**Revlimid**
PFS rate, n(%)	39(43.8)	17(34.7)	22(55.0)	9(29.0)	6(37.5)	3(20.0)
PFS time (months)						
Median (SE)	29.2(4.9)	30.3(3.8)	22.7 (7.0)	26.4(6.5)	38.1(12.1)	20.1(0.9)
95% CI (LB-UB)	19.5-38.9	22.0-37.7	8.9-36.4	13.6-39.1	14.4-61.9	18.2-22.0
Log Rank (Mantel-Cox) *P* value	0.827			0.147		

PFS = Progression-free survival; SE = Standard error; CI = confidence interval; LB = lower bound; UB: upper bound.

Table 4 Overall Survival Outcome

	Median follow up (mo)	OS rate (%)	OS time (mo)	
			Mean (SE)	95% CI (LB-UB)
Total (n = 184)		77.7	123.5(11.5)	100.8-146.1
Revlimid (n =74)	41.9	83.8	122.3(8.9)	104.8-139.8
Rivelime (n = 110)	47.6	73.6	123.3(14.2)	95.4-151.2
P (Log-rank Mantel-Cox)	0.060	0.105	0.484	

OS = Overall survival; SE = Standard error; CI = confidence interval; LB = lower bound; UB = upper bound

the addition of ixazomib to a Rd regimen was reported to be associated with significantly longer PFS (20.6 months vs. 14.7 months) with limited additional toxic effects (higher frequency of grade 3-4 thrombocytopenia) in the ixazomib group.[18] In the ASPIRE trial with 792 RRMM patients who received carfilzomib with Rd (carfilzomib group) or Rd alone (control group), the addition of carfilzomib to Rd resulted in significantly improved PFS (median 26.3 vs. 17.6 months) and 24-month OS rate (73.3% vs. 65.0%) as well as a favorable risk-benefit profile with similar rates of grade ≥3 AEs (83.7% and 80.7%, respectively) and AE-related treatment discontinuation (15.3% and 17.7%, respectively).[16]

In addition, the most common toxicities of lenalidomide in RRMM patients were reported to be hematological in nature, including neutropenia (grade 3/4 25%-40%), anemia (grade 3/4

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Figure 2 Kaplan Meier analysis for overall survival (OS) in relapsed/refractory multiple myeloma patients treated with brand-name lenalidomide (Revlimid) versus generic equivalent (Rivelime).

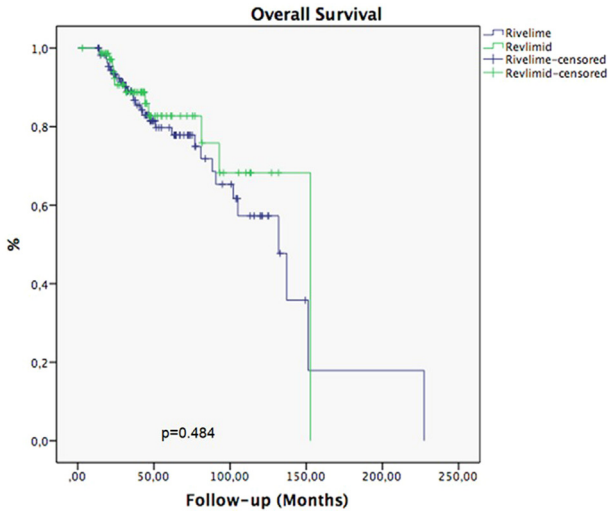


Table 5 Safety Data

Adverse events, n(%)		Revlimid (n = 74)	Rivelime (n = 110)	*P* Value
Grade≥3 hematologic toxicity	Total	19 (25.7)	15 (13.6)	.021
	Second line therapy	5 (6.8)	5 (4.6)	.215
	Third line therapy	4 (5.4)	4 (3.6)	.254
	≥4 lines of therapy	1 (1.4)	5 (4.6)	.564
	Maintenance	9 (12.2)	1 (0.9)	<.001
Any grade non-hematologic toxicity		**Revlimid (n = 74)**	**Rivelime (n = 110)**	
Fatigue		38 (51.4)	58 (52.8)	
Diarrhea		27 (36.5)	41 (37.2)	
Muscle weakness		25 (33.8)	36 (32.7)	
Rash		26 (35.1)	43 (39.1)	
Peripheral neuropathy		14 (18.9)	23 (20.9)	
Venous thromboembolism		2 (2.7)	7 (6.4)	
Pneumonitis		24 (32.4)	33 (30.0)	
Outcome, n(%)		**Revlimid (n = 74)**	**Rivelime (n = 110)**	
Treatment discontinuation, n(%)		23 (31.1)	32 (29.1)	
Dose change, n(%)		19 (25.7)	42 (38.2)	

9%-26%), thrombocytopenia (grade 3/4 11%-15%) in the MM-009, MM-010 and MM-021 studies.[8-10]

Notably, in a past study with 98 RRMM patients on Rd regimens based on original and generic lenalidomide, the authors reported similar rate of hematologic AEs, whereas a lower rate of some non-hematologic AEs and a higher rate of pyrexia (as a grade 3-4 AE) in patients who received original versus generic form of lenalidomide.[6] Our findings revealed similar rate of nonhematological AEs, treatment discontinuation due toxicity (31.1% and 29.1%) and myelosuppression in particular (25.7% and 20.0%) between original and generic forms of lenalidomide, whereas a likelihood of higher rate of Grade ≥3 hematologic toxicity in the original form. Nonetheless, it should be noted that the lenalidomide-containing regimens were not limited to doublet Rd regimen in our study, with use of singlet or Rd-based triplet regiments in at least half of patients.

Given a shift toward the use of extended treatment in RRMM to further improve long-term outcomes, additional effective agents are considered to have acceptable side-effect profiles to enable patients to continue receiving therapy for prolonged periods.[18,20] In this regard, our findings support that the AE profile of lenalidomide, regardless of the use of original or generic form, is manageable with minimal cumulative toxicities enabling long-term therapy along with the low risk of thrombosis and neuropathy.[4,6,21] Identification of the generic alternative (Rivelime) to be as effective and tolerable

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as the brand-name Revlimid and to yield similarly improved survival over a median 40-month of follow up in our RRMM patients seem also notable given the potential cost-savings related to long-term treatment with lenalidomide-containing regimens.

Certain limitations to this study should be considered. First, due to the retrospective single-center design of the present study, establishing temporality between the cause and effect is not possible and our subjects may not represent the general population due to the small sample size. Second, lack of data on certain patient reported outcome measures related to quality of life is another limitation, which would otherwise extend the knowledge achieved in the current study. Nonetheless, despite these limitations, the current study is the first study to compare original and generic lenalidomide in the settings of singlet, Rd-doublet and Rd-based triplet regimens in RRMM patients and in terms of not only efficacy and safety parameters but also the survival outcome.

Conclusion

In conclusion, our findings in RRMM patients receiving singlet, doublet (Rd) or triplet (Rd plus carfilzomib, ixazomib or bortezomib) lenalidomide containing regimens revealed similar efficacy and safety profile and similar survival outcome between the original and generic lenalidomide. Accordingly, replacing Revlimid with its generic version Rivelime in singlet, doublet or triplet lenalidomide containing RRMM regimens seems not to compromise the efficacy of treatment, and to yield a similarly improved response rates and survival outcome along with no additional toxic effects, enabling a long-term therapy. These findings seem notable given that generic medicines, apart from being safe and effective as their branded counterparts, have also been associated with further advantage of cost-effectiveness. The efficacy and safety profile of original and generic lenalidomide should be further explored by larger population-based studies with a longer follow up to better demonstrate the survival benefit of generic lenalidomide.

Clinical Practice Points

- **What is already known about this subject?** The efficacy of lenalidomide, a tumoricidal immunomodulatory drugs with antiproliferative, pro-apoptotic and anti-angiogenic effects on plasma cells, has been shown in patients with relapsed/refractory multiple myeloma (RRMM). However, no studies to date investigated the comparative efficacy, safety and survival outcome with use of original versus generic lenalidomide containing regimens in RRMM patients.
- **What are the new findings?** Our findings in RRMM patients receiving singlet, doublet (Rd) or triplet (Rd plus carfilzomib, ixazomib or bortezomib) lenalidomide containing regimens revealed similar efficacy and safety profile and similar survival outcome between original and generic lenalidomide.
- **How might it impact on clinical practice in the foreseeable future?** Replacing Revlimid with its generic version Rivelime in singlet, doublet or triplet lenalidomide containing RRMM regimens seems not to compromise the efficacy of treatment, and to yield a similarly improved response rates and survival outcome along with no additional toxic effects, enabling a long-term therapy. These findings seem notable given that generic medicines, apart from being safe and effective as their branded counterparts, have also been associated with further advantage of cost-effectiveness.

Disclosure

The authors declare that they have no conflict of interest.

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