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RESEARCH

Efficacy of everolimus plus hormonal treatment after cyclin-dependent kinase inhibitor; real-life experience, A TOG study

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Abstract

Purpose In advanced breast cancer, endocrine therapy is preferred in the absence of visceral crisis. Cyclin-dependent kinase inhibitors (CDKi) are the gold standards. The selection of subsequent treatments after CDKi treatment is still controversial, and the efficacy of everolimus (EVE) combinations is unknown. In this study, we aimed to investigate the efficacy of EVE after CDKi administration in real-life experiences.

Method The study received data from 208 patients from 26 cancer centers. Demographic and histologic features, diagnosis, progression, last visit dates, and toxicities were recorded. This study was a retrospective case series.

Results One hundred and seven patients received palbociclib, while 101 patients received ribociclib as a CDKi. The overall response and disease control rates of EVE combinations were 60% and 88%, respectively. In univariate analysis, the absence of liver metastasis, age > 40 years, better type of response, and immediate treatment after CDKi were related to increased progression-free survival. Liver metastasis and response type were significantly associated with overall survival. In the multivariate analysis, response remained significant in terms of progression-free survival, while response type, liver metastatic disease, and hematologic toxicity were prognostic in terms of overall survival.

Conclusion This study provides evidence of the benefits of EVE combinations after CDKi treatment. EVE combinations may be more appropriate for patients with non-liver metastasis, and the first treatment response shows the benefit of treatment. In addition, immediate treatment after CDKi treatment is more beneficial than later lines of treatment.

Keywords Everolimus · Breast cancer · Cyclin-dependent Kinase Inhibitors · Palbociclib · Ribociclib · Life experience

Introduction

Advanced breast cancer patients without life-treating visceral crisis tend to be treated with endocrine therapy for as long as possible. Endocrine therapy has fewer side effects than chemotherapy. In addition, endocrine therapy is a valuable option for patients who respond to chemotherapy [1, 2]. Nearly 75% of advanced breast cancers are hormone receptor-positive and treated with endocrine agents. Primary and secondary endocrine resistance are common problems that require treatment [3, 4]. Novel therapies based on cyclin-dependent kinases 4/6 (CDK4/6) have been approved and used since 2017, according to the results of PALOMA-2 and PALOMA-3 studies. New combinations have emerged with MONARCH-2 and MONARCH-3 containing abemaciclib. These drug combinations have become the first-line standards of care worldwide [5–9]. Although CDK4/6-based treatments are effective, their possible resistance mechanisms remain unclear. One possible mechanism is activation of phospoinositide3-kinase (PI3K)/AKT/mammalian target

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of rapamycin (mTOR), which is inhibited by everolimus (EVE) [10, 11]. In the presence of endocrine therapies (ET), tumor cells may adopt alternate pathways, such as the mTOR pathway, which may contribute to the development of ET resistance [12]. The effectiveness of ET and oncological outcomes in patients with HR + and HER2-metastatic breast cancer are, therefore, thought to be improved by co-targeting both signaling pathways by dual inhibition with ET and an mTOR inhibitor [12, 13]. At a median follow-up of 18 months, the BOLERO-2 study demonstrated that EVE plus exemestane (EXE) increased the median progression-free survival (PFS) in comparison to placebo (PBO) plus EXE while preserving health-related quality of life (HRQoL) [14, 15]. A small number of studies have examined real-world experience with the use of EVE-EXE combination therapy in unselected groups of advanced HR+, HER2− MBC patients, despite potential differences in baseline characteristics and treatment responses of patients recruited in clinical trials and those treated outside clinical trials [16–18]. In recent studies, a new molecule called alpelisib, which targets the mTOR pathway, has been approved in patients with advanced breast cancer [19]. There is no clear evidence of treatment selection after treatment with CDK4/6 inhibitors (CDKi). Multiple options have shown different benefits following CDKi treatment [20].

There is a lack of information on the choice of treatment alternatives and effectiveness of follow-up therapies (continuing endocrine therapy while using a drug via a different mechanism or moving to chemotherapy). We investigated the efficacy of EVE-containing regimens after CDKi administration in real-life practice.

Material method

Study population

This study was approved by the 18th Turkish Oncology Group Congress. After the study was approved, the database was shared with volunteer centers. This study included 208 patients from 26 cancer centers. Only patients who received everolimus exemestane or everolimus fulvestrant after a CDKi with hormonal treatment were included in the study. Demographic information, diagnosis date, age, stage, last visit, and date of exitus were recorded. Tumor features were also evaluated. Estrogen, progesterone, HER-2 and Ki-67 levels were evaluated. Metastatic sites and CDKi start and cessation dates were recorded. CDKi and everolimus treatment lines were determined and compared. The best responses to everolimus combinations, PFS, dose reduction, and major adverse events were recorded.

Statistics

Statistical analyses were performed using SPSS (version 22.0; IBM Corp., Armonk, NY, USA). SPSS Inc, Chicago, IL). The Kolmogorov–Smirnov test was used to determine whether the data conformed to a normal distribution. Descriptive data were presented as either means or medians for continuous variables, and frequencies and percentages were reported for categorical variables. Kaplan–Meier curves were used to determine the differences in survival. Chemotherapy responses were defined based on the radiological reports. Differences between groups were tested using the chi-square test. Cox regression analysis was performed to evaluate the prognostic factors. These factors could not converge or were outfitted in the analysis.

Results

Patient characteristics

The median patient age was 58 years. Of the 208 participants, only one male patient was included in the study. Seventy-six patients had de novo metastasis, while 132 had relapsed disease. The percentages of bone, lung, liver, and brain metastases were 83.6, 41.9, 33.8, and 9.4%, respectively. One hundred and seven patients received palbociclib, whereas 101 patients received ribociclib prior to everolimus treatment. The median number of lines of CDKi and everolimus were 2 and 3, respectively. Two-thirds of the patients received everolimus immediately after CDKi treatment, while one-third had received other treatments in between. The rates of EXE and fulvestrant use in EVE-receiving patients were 92.2% and 7.8%, respectively. The response rate for EVE treatment was 60%, and disease control rates were determined. 88%. The characteristics of the study population described in Table 1.

The highest toxicity observed in the study population was stomatitis, followed by hematologic adverse events. No non-infectious pneumonitis was evaluated because of the low record quality. The detailed profiles are described in Table 2.

Survival

The median overall survival (OS) in the entire study group was 38 months, with a follow-up period of 49 months. The median PFS times for CDKi and EVE were 11 and 4 months, respectively. There was no correlation in PFS with CDKi- and EVE-based treatment. ($p = 0.23$) There was no difference in PFS initial diagnosis type of cancer. The median PFS was 5 months and 6 months in patients with recurrent

Table 1 The features of study population

Patient characteristic	Number of patients (%)
Age median (range)	58 (27–86)
Breast cancer type	
De novo metastatic	76 (36.5)
Recurrence	132 (63.5)
Metastatic sites	
Bone	173 (83.6)
Lung	85 (41.9)
Liver	69 (33.8)
Brain	19 (9.4)
CDKi line	
1st	82 (39.4)
2nd	67 (32.2)
3rd	31 (14.9)
CDKi type	
Ribociclib	101 (48.6)
Palbociclib	107 (51.4)
Everolimus line	
2nd	48 (23.1)
3rd	66 (31.7)
4th	46 (22.1)
Everolimus combination	
Aromatase inhibitor	192 (92.3)
Fulvestrant	16 (7.7)
Best response	
CR	71 (38.4)
PR	54 (29.2)
SD	60 (32.4)
Everolimus dose reduction	
No	150 (77.3)
Yes	44 (22.7)

Table 2 Toxicity profile of everolimus combination in study population

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic	120 (60.9)	41 (20.8)	28 (14.2)	7 (3.6)	1 (0.5)
Hepatoxicity	137 (69.9)	34 (17.3)	19 (9.7)	6 (3.1)	-
Stomatitis	81(41.1)	51 (25.9)	46 (23.4)	17 (8.6)	2 (1)
Hyperlipidemia	151 (78.2)	27 (14)	11 (5.7)	4 (2.1)	-
Hypertension	163 (83.2)	26 (13.3)	6 (3.1)	1 (0.5)	-

and de novo metastatic disease, respectively. ($p=0.6$) There was a significant difference between in patients younger and older than 40 years old. ($p=0.027$) Younger patients had 4 months of PFS while older patients had 6 months. There was no difference in the PFS between patients younger and older 65 years. ($p=0.61$) Liver metastasis was significantly associated with PFS ($p<0.001$). Absence of liver metastasis had a 7 months of PFS while liver metastatic disease had a PFS of 4 months. (Fig. 1) Lung, brain, and bone metastases had no effect on the PFS. There was no difference in PFS according to the type of prior CDKi used. ($p=0.20$) Increased PFS was observed after the immediate use of everolimus after CDKi. ($p<0.001$) (Fig. 2) The median PFS was 8 vs. 5 months. There were statistical differences in PFS according to the grades of adverse events such as stomatitis, hyperlipidemia, hematologic toxicity, hepatotoxicity, and hypertension. ($p=0.006$, $p=0.026$, $p<0.001$, and $p=0.018$, respectively). Dose reduction had no effect on PFS. ($p=0.80$) There was a significant difference in PFS due to the best response of everolimus treatment. ($p<0.001$) Complete response (CR), partial response (PR) and stabile disease had median PFS of 9, 6 and 3 months respectively.

There was no difference in overall survival (OS) in terms of the initial disease status. ($p=0,71$) There were difference due to metastatic sites except liver metastasis. ($p<0.001$) The median OS was 22 versus 9 months favoring absence of liver metastatic disease. (Fig. 3) No difference was observed in OS due to CDKi type. ($p=0.57$) The OS was significantly different due to best response. ($p<0.001$) The median OS was not reached in CR and PR while 8 months of OS was determined in SD group. (Fig. 4) Hematologic toxicity and hepatotoxicity had prognostic effects in terms of OS ($p<0.001$; $p<0.001$), and OS was inversely correlated with the grade of adverse events. Dose reduction with everolimus had no effect on patient survival. ($p=0.60$).

In multivariate analysis, only the best response was an independent risk factor for PFS. ($p<0.001$) In terms OS, liver metastasis, best response and hematologic toxicity remained significant. ($p=0.031$; $p<0.001$; $p<0.007$) The risk factors for both PFS and OS are described in Table 3.

Discussion

Our study showed that EVE combinations are effective treatment options with considerable prolongation of PFS, even after treatment with CDKi. Immediate treatment after CDKi was determined to have a better PFS than later lines of treatment. Moreover, the best response and liver metastasis may have both predictive and prognostic effects in EVE treatment.

In a study evaluating 13 patients who received EVE combinations after CDKi treatment, the median PFS was reported to be 9 months with 37.4 months of OS [21]. Our data showed 9 months in the PFS only CR group, while PR and SD groups had shorter PFS. Compared with this small study, our study demonstrated nearly the same OS in the entire study group. In a recently published study investigating subsequent treatments after CDKi, Karacin et al.

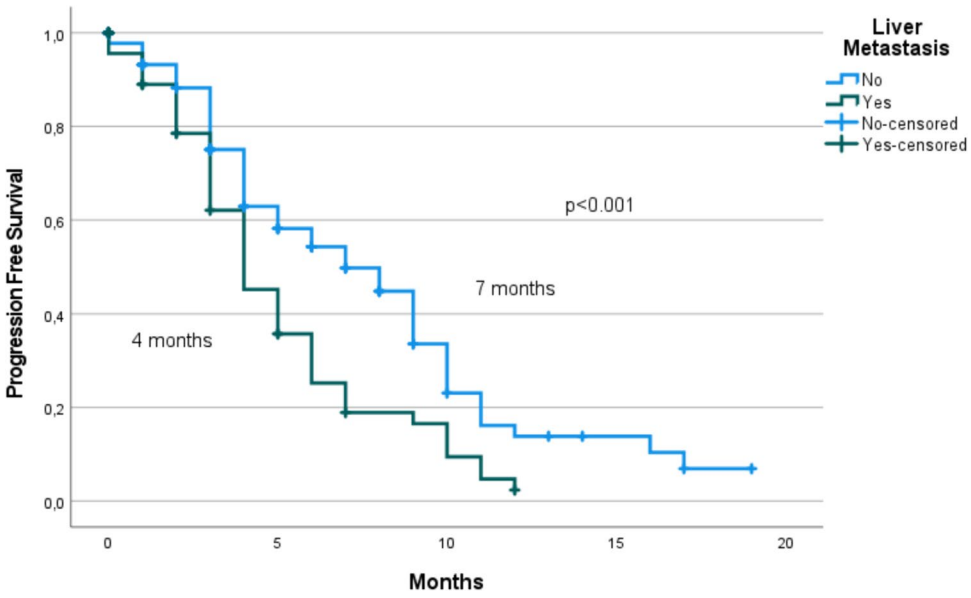

Fig. 1 The difference of PFS in patients according to liver metastasis

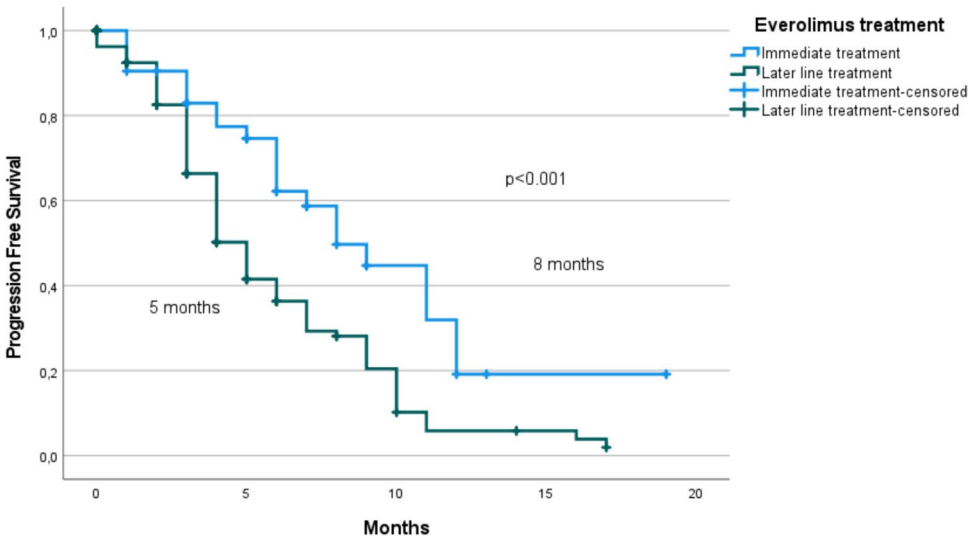

Fig. 2 The difference in PFS in immediate or later line after CDKi in everolimus treatment

reported that endocrine treatments, including EVE combinations, had better outcomes in the first-line treatment. After the second- and third-line usage of CDKi, hormonal treatments, including EVE-EXE, had similar outcomes to chemotherapy [20]. Similar to the data reported by Karacin et al., our study showed that there was no relationship between PFS with CDKi and EVE-based treatment.

Our study adds to this literature, as EVE-based treatments are more effective immediately after CDKi. The efficacy of EVE significantly decreased when it was postponed to later lines. Cook et al. reported that the prior use of CDKi is not related to the decreased efficacy of EVE-based treatment [22]. In addition, the EVERMET study comparing EVE efficacy in terms of prior CDKi use showed that EVE treatment was less effective after CDKi. The longest PFS was observed with first-line EVE [23]. The main mechanism may be related to increased endocrine resistance in the later lines. This phenomenon was also reported by Mo et al. In a study comparing EVE-based treatment prior to CDKi use, increased lines of treatment until EVE were related to decreased efficacy. In addition, this study found that prior CDKi use was related to the decreased efficacy of EVE. The fifth or more lines of EVE treatment were related to a two-fold increase in the risk of death [24]. In a prior TOG study evaluating EVE-EXE treatment without prior CDKi declared 8 months [18]. Our study showed that a median PFS of 4 months was compatible with the decreased PFS after CDKi when compared to this study. In a population-based exploratory analysis, EVE-based treatments were reported to have better outcomes in subsequent studies.

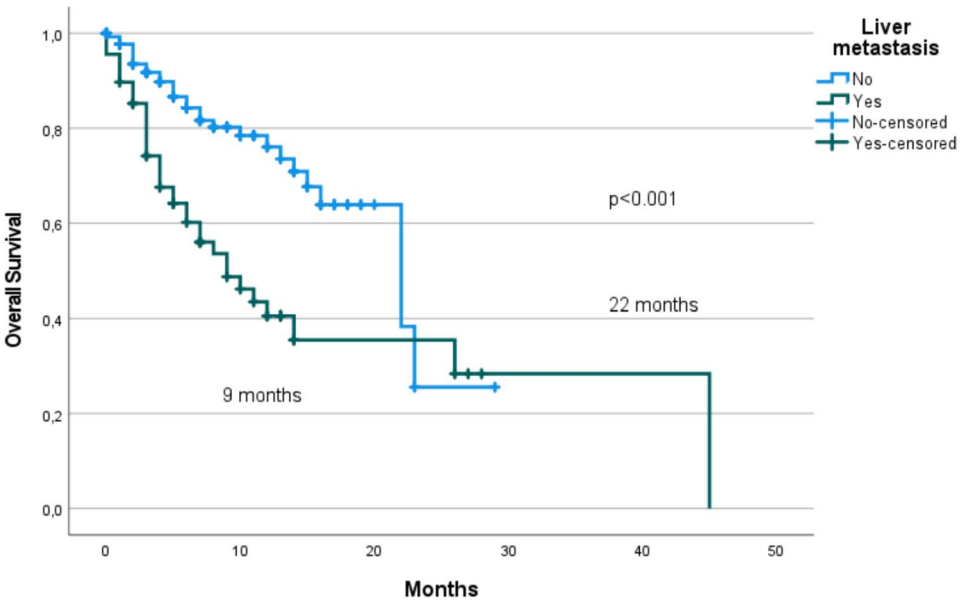

Fig. 3 OS according to liver metastatic disease

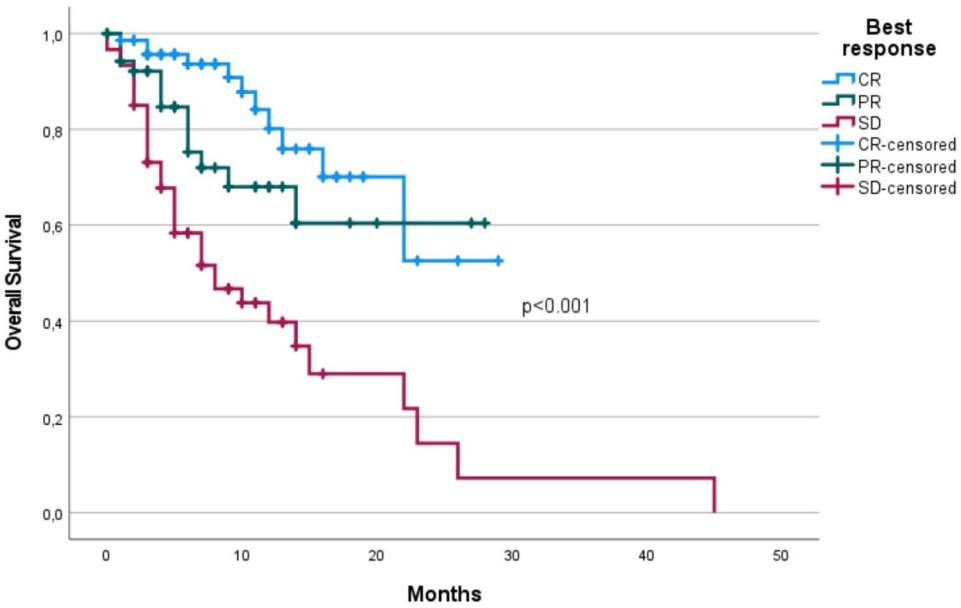

Fig. 4 The difference in terms of OS according to best response

Although first- and second-line treatments are useful, more benefits were observed in patients who received third-line treatment or beyond. This study had a very long inclusion period, including both the pre- and post-CDKi era. Some patients received a CDKi after EVE treatment [25].

Our study showed no differences between CDKi types. The doses of palbociclib and ribociclib were nearly equal in the study population. No difference in OS and PFS was observed according to prior CDKi type. There was heterogeneity in real-life studies according to the countries' drug approval. None of the patients used abemaciclib because of its unavailability in Turkey. Real-life studies confirmed the equal efficacy of palbociclib and ribociclib in patients who are treated before everolimus [26]. In the studies by Mo et al., Kitano et al., and Dhakal et al., nearly all patients received palbociclib [21, 24, 27]. Other large observational studies have not investigated CDKi type and effect of CDKi on EVE treatment [22, 25].

Bilici et al. found that bone-only disease had better outcomes with EVE-EXE treatment [18]. Liver metastasis was associated with worse outcomes after CDKi treatment in our study. This phenomenon may be related to a more aggressive tumor behavior with an increased line of treatment and subsequent liver metastasis after CDKi treatment. Mo et al. reported more liver metastatic patients

Table 3 The multivariate analysis of risk factors for PFS and OS

Factor	PFS				OS			
	HR	Confidence Int		*p* value	HR	Confidence Int		*p* value
Age	0.99	0.97	1.01	0.70	1.01	0.98	1.04	0.35
Diagnosis status	1.14	0.73	1.80	0.54	0.59	0.32	1.11	0.10
ER	1.00	0.98	1.01	0.97	1.00	0.98	1.01	0.99
Lung met	0.95	0.62	1.47	0.83	0.60	0.31	1.13	0.11
Liver met	0.92	0.58	1.47	0.75	***1.98***	***1.06***	***3.67***	***0.031***
Bone met	0.86	0.47	1.56	0.62	2.23	0.93	5.35	0.07
Brain met	0.57	0.26	1.24	0.16	1.81	0.74	4.41	0.19
CDKi line	0.89	0.53	1.49	0.67	0.88	0.49	1.59	0.67
CDKi type	0.90	0.58	1.38	0.63	0.77	0.40	1.47	0.43
Everolimus line	1.16	0.71	1.89	0.53	1.30	0.77	2.19	0.32
Best response	***2.78***	***2.05***	***3.76***	***< 0.001***	***2.78***	***1.84***	***4.20***	***< 0.001***
Dose reduction	0.87	0.51	1.48	0.61	0.66	0.30	1.44	0.30
Hematologic Tox	1.22	0.96	1.55	0.10	***1.58***	***1.13***	***2.20***	***0.007***
Hepatic Tox	1.11	0.83	1.49	0.44	1.04	0.73	1.49	0.79
Stomatitis	0.97	0.76	1.23	0.81	1.14	0.83	1.57	0.39
Hyperlipidemia	1.05	0.70	1.58	0.78	1.29	0.76	2.16	0. 33
Hypertension	1.11	0.64	1.91	0.69	0.84	0.44	1.60	0.60
Immediate treat	1.33	0.58	3.02	0.49	0.58	0.20	1.62	0.30

ER estrogen receptor, *Tox.* toxicity, *Treat.* treatment, *Int* interval, *PFS* progression free survival, *OS* overall survival

after CDKi treatment, but increased OS was observed in patients with bone-only non-visceral metastases [24].

In network analysis, mTOR inhibitors in combination with AI and fulvestrant were reported to be better options with CDKi and PI3K inhibitors than fulvestrant-only treatment [28]. Our study showed no differences in terms of the combination of EVE with AI or fulvestrant. There was a small proportion of fulvestrant treatment compared to exemestane treatment, which made our data inconclusive.

Limitations

The study had a retrospective design, which reduced the data quality. No patient was treated with abemaciclib due to approval in Turkey. Very few pneumonitis records could not be analyzed. There were a limited number of patients who received fulvestrant in combination with EVE, which made these data inconclusive.

Conclusion

This study provides evidence of the benefits of EVE combinations after CDKi treatment. EVE combinations may be more appropriate for patients with non-liver metastasis, and the first treatment response shows the benefit of treatment. In addition, immediate treatment after CDKi treatment is more beneficial than later lines of treatment.

Clinical Practice Points.

- Everolimus combinations are effective treatment options after CDKi.
- Everolimus combinations are more effective in the absence of liver metastasis
- Type of previous CDKis are not effective in efficacy of Everolimus combinations.
- Everolimus combinations are more effective when used immediately after CDKi.
- Best response to Everolimus treatment is a predictive factor.

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Author contributions IB: Idea, statistics, data collection, writing, critical evaluation, HD: supervision, critical evaluation; all other: data collection

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Data availability The data is available if requested.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval This study was approved by the local ethics committee of Afyonkarahisar Health Sciences University and the trial was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Turkish Drug and Medical Device Organization. The manuscript revised with Paperpal AI for grammar and punctuational errors.

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