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Evaluating the Efficacy and Safety of PARP Inhibitors in BRCA-Mutated Triple Negative Breast Cancer- A Systematic Review

Olakunle Michael Surulere

ABSTRACT:

Introduction: TNBC is a subtype of breast cancer that accounts for 10-15% of instances and is distinguished by the lack of HER2 overexpression, progesterone receptors, and oestrogen receptors. Compared to other kinds of breast cancer, TNBC is more aggressive, has a worse prognosis and survival rate, and can only be treated with chemotherapy. In cancer cells with BRCA mutations, PARP inhibitors target the PARP enzyme in DNA repair, accumulating DNA damage and causing cell death. The objective of a systematic review was to assess the efficacy and safety of PARP inhibitors in the management of TNBC with BRCA mutations. Objective response rates and outcomes like overall survival and progression-free survival were evaluated.

Methods: The purpose of the systematic review is to evaluate how well PARP inhibitors, work to treat triple negative breast cancer. The Cochrane library and PubMed were searched for pertinent research, and the search period was from 2012 to 2022. Phase 2 and 3 randomised clinical trials examining the effectiveness of PARP inhibitors alone or in combination with other treatments and reporting progression-free survival, overall survival, and objective response rate met the inclusion criteria for the studies. Preclinical studies, single-arm studies, trials without information on BRCA status, case reports, and studies conducted in languages other than English were excluded. The JADAD score was used to evaluate the trials that were chosen. Patient characteristics, treatment modalities, and efficacy results were among the data retrieved from the research.

Results: When compared to the control group, patients using PARP inhibitors demonstrated statistically significant improvements in progression-free survival (PFS). However, there were no appreciable differences in overall survival (OS). The effectiveness of the PARP inhibitors varied among patient demographics and subgroups. Anemia, tiredness, and nausea were the most often reported side effects. In comparison to the control group, veliparib was linked to a greater incidence of anaemia and nausea. In both groups, a similar number of patients experienced serious adverse effects.

Discussion: The effectiveness of PARP inhibitors as monotherapy or in combination with carboplatin-paclitaxel has been shown in evaluated studies. Anemia, tiredness, and nausea were the most frequent adverse effects, and severe hematologic toxicities were of particular concern. However, future negative outcomes can be avoided by routine blood counts and the restriction of some PARP inhibitors to individuals who have recovered from hematologic toxicity. Patients with mutations in particular HR-related genes did not react to olaparib therapy, however some subsets of breast cancer and other cancers such as prostate cancer, may respond favourably to PARP inhibitors. The systematic review has shortcomings such research diversity and a dearth of trials with sufficient power, which can reduce the dependability of results.

Conclusion:PARP inhibitors have been proven in clinical trials to be beneficial in treating BRCA mutant TNBC, resulting in objective responses and complete/partial remissions. They have a good safety profile, with the majority of side effects being mild to moderate. Despite the increased risk of myelosuppression, PARP inhibitors are a viable treatment option for patients with BRCA mutant TNBC. More research is required to completely comprehend optimal use and long-term advantages.

KEYWORDS: PARP, Olaparib, Objective response rate, Progression Free Survival

INTRODUCTION

Breast cancer (BC) is the world's second frequently diagnosed cancer and the leading widely known malignancy in women(1, 2). Men make up less than 1% of BC patients(1-3). Despite improving survival rates, breast cancer remains the fourth leading cause of cancer-related death(4). An estimated 627,000 deaths were said to have occurred among women diagnosed with BC in 2018(4, 5). About 10-15% of all occurrences of breast cancer are TNBC, with an earlier average age at of presentation (1, 4). It manifests in a more aggressive manner, frequently metastazing to other sites in the body, and has a poor prognosis and a lower survival rate. TNBC is unaffected by hormonal therapy or treatments that target the HER2 receptor(2, 4, 5). TNBC is more likely to occur in people with mutation of BRCA1/BRCA2, making these mutations a potential marker for individualised treatment (1, 6). TNBC is characterized by the absence of estrogen and progesterone receptors, as well as by the lack of HER2 overexpression or

amplification, and accounts for around 15% of all breast cancer cases(6,7). TNBC can only be treated with chemotherapy, unlike breast tumours that are HER2 or estrogen positive (5, 10).

PARP ACTION

BRCA 1 and 2 tumour suppressor genes are responsible for the production of certain encoding proteins responsible for fixing damages in double stranded DNA and this is achieved through the homologous recombination repair pathway(29). The PARP family of enzymes are crucial in the single stranded DNA damage repair pathway(15, 29). In laboratory studies, cells lacking functional BRCA1 or BRCA2 are highly sensitive to PARP inhibition. This sensitivity is believed to stem from a combination of factors, such as unresolved DNA damage causing synthetic lethality and PARP trapping physically obstructing replication forks, leading to replication arrest(15, 29, 30).

The PARP enzyme is responsible for identifying and repairing single-stranded breaks in DNA. PARP inhibitors work by targeting the PARP enzyme and disrupting its ability to repair DNA, leading to an accumulation of DNA damage and triggering cell death through a process known as apoptosis (5, 11, 18). In breast cancer cells with BRCA mutations, PARP inhibitors take advantage of the cells' faulty DNA repair mechanisms, causing significant DNA damage and selectively killing cancer cells while leaving normal cells unharmed (5, 8, 14, 15). Clinical trials on breast tumors with BRCA mutations have shown that PARP inhibitors can be a viable therapy option as these types of cancer cells do not respond to conventional treatments (11, 14, 17). Therefore, summarizing the available research data on PARP inhibitors is important for guiding treatment decisions by clinical practitioners.

The aim of the systematic review was to evaluate the safety and effectiveness of PARP inhibitors in the management of BRCA mutated triple negative breast cancer patients (TNBC), as measured by outcomes such as overall survival (OS), progression-free survival (PFS), and objective response rates (ORR).

METHODS

Search strategy

A thorough search of peer-reviewed literature was conducted for this systematic review, and the most recent data were gathered from the Cochrane library and PubMed. The search, which was done on November 27, 2022, covered all works released in the previous ten years (2012-2022). Free full-text publications, abstracts, clinical trials, randomised controlled trials, and pertinent search terms and their synonyms were included in the search criteria. These terms included "Breast cancer," "TNBC," "Invasive ductal carcinoma," "BRCA," "germline BRCA," "Breast Tumor," "Olaparib," "Veliparib," "Clinical trial," "Randomized clinical trial," and "RCT" in PubMed and the Cochrane. The search strategy with Boolean operators were ((PARP OR OLAPARIB OR VELIPARIB) AND (TNBC OR GERMLINE BRCA OR BREAST CANCER OR METASTATIC BREAST CANCER OR TRIPLE NEGATIVE BREAST CANCER OR MALIGNANT BREAST CANCER)) AND (CLINICAL TRIAL OR RCT OR RANDOMISED CLINICAL TRIAL).

Inclusion criteria

The inclusion criteria for this review consisted of randomized clinical studies that investigated the effectiveness of PARP inhibitors (Veliparib, olaparib, talazoparib) either alone or in combination with other treatments in patients with metastatic breast cancer. The studies included in the review were phase 2 and 3 randomized controlled trials that evaluated outcomes such as objective response rate, progression-free survival, overall survival, and safety. The papers considered for the review were limited to those written in English and were only full-text randomized controlled trials that met all of the aforementioned criteria.

This review only considered studies that met set criteria and excluded the following types of studies: (1) studies on cell cultures or animals, (2) studies that only had one group of patients, (3) studies that did not include information on BRCA mutations or homologous recombination deficiency, (4) single case reports, (5) trials of treatment given before surgery, (6) trials done before 2012, (7) animal or non-human studies, and (8) studies not published in English.

Outcome

The study will measure the following endpoints at 95% confidence intervals: progression-free survival (in months), overall survival (in months), and objective response rate (as a percentage). The results are considered statistically significant if the p-value is less than 0.05. The incidence of adverse events will also be recorded for each study.

Data extraction

The data was collected based on the set criteria for inclusion and exclusion and was verified by reading the titles, abstracts, and complete texts, as necessary. Information was gathered from each eligible randomized controlled trial and included the author's name, year of publication, number of participants, study design, patient demographics, treatment methods, efficacy outcomes such as overall survival, objective response rate, and progression-free survival, and the frequency of adverse events.

Risk of Bias

In this systematic review, the JADAD score was utilised to assess the methodological quality of the selected RCTs (13). The publications were evaluated based on the presence of three basic clinical trial methodological elements: randomization, masking, and patient accountability, including withdrawals (13). For a total score of 0-5, one point is added for each "yes" answer to the first five questions, and one point is subtracted for each "yes" answer to the final two questions. However, a score of 2 or higher is generally considered to indicate a trial of moderate quality, while a score of 3 or higher is considered to indicate a high-quality trial(13).

RESULTS

The comprehensive database and registers search yielded 359 studies. After eliminating duplicates, 224 studies were evaluated based on their titles and abstracts. 30 studies were further evaluated for eligibility by reviewing their full text. Unfortunately, the full text of 16 studies was not available, four studies did not measure comparable outcomes and 4 studies had paid access restrictions (Fig 1). Ultimately, 6 studies (14), (15), (16), (17), (18), (19) containing 3166 patients were deemed suitable for further analysis and the features of these studies can be found in Table 1.

Three of the four included studies looked at the outcomes of olaparib [14, 15, 16], two at talazoparib [17, 19], and one at veliparib [18]. PARP inhibitors were administered as a single treatment in five of the studies, with control agents such as capecitabine, eribulin, gemcitabine, and vinorelbine. Only one of the studies under focus examined the use of PARP inhibitors in conjunction with carboplatin-paclitaxel vs placebo+carboplatin-paclitaxel. The quality of the relevant studies assessed by the JADED score can be seen in Fig. 2, while one study was assessed using Newcastle Ottawa score.

Efficacy outcomes (PFS, ORR, OS, DFS)

These studies reported results of clinical trials comparing the effectiveness of the PARP inhibitor (olaparib, talazoparib, and veliparib) to either a standard therapy or placebo. The results showed a significant improvement in progression-free survival (PFS) for patients taking PARP inhibitors compared to those in the control group with a statistical significance of <0.001(14, 15, 17, 19) in four studies and 0.004 in one study(18). However, the overall survival (OS) did not differ significantly between groups in most trials. There were some differences in results between trials, with the PARP inhibitors showing varying degrees of efficacy in different patient populations and subgroups- the Asian study by Lee et al (2021) reports an improvement in median PFS which was 9.0 months in the Talazoparib group vs 7.1 months for chemotherapy (hazard ratio [HR], 0.74 [95% CI, 0.22 to 2.44]), a higher objective response rate (62.5% [95% vs. 25.0%) and a Median overall survival of 20.7 months versus 21.2 months (HR, 1.41 [95% CI, 0.49 to 4.05]). In some trials, PFS was longer in the PARP inhibitor group and response rates were higher, while in others, there was no significant difference in OS. Litton et al (2020) also examined multiple subtypes of breast cancer and found that responses occurred in 4 of 6 (67%) patients with triple-negative breast cancer (TNBC), 12 of 20 (60%) patients with ER+ HER2-negative illness, and in one patient with HER2-positive BC (17).

Safety outcomes and adverse effects

The studies report on the safety outcomes of patients who received olaparib, talazoparib, veliparib, or placebo as part of these clinical trials. Olaparib was generally well-tolerated, with the most common adverse events (AEs) being anemia and decreased neutrophil count, with fatigue and lymphopenia being less common. Blood transfusions were required in a small number of patients. Talazoparib was also well-tolerated with AEs consistent with other primary analysis (31). Anemia was the most common AE for all the PARP inhibitors in focus, followed by fatigue and nausea. Veliparib was associated with a higher rate of anemia, thrombocytopenia, nausea, and diarrhea compared to the control group. Serious AEs occurred in a similar number of patients in both groups. There were also occurrences of decreased neutrophil and white cell count, but these were of grade 3 or higher in less than 1% of patients. In the study, the median relative dose of talazoparib was found to be higher in the Asian subgroup as compared to the overall group of patients in terms of safety. However, the median relative dose of chemotherapy was found to be similar between the Asian subgroup and the overall patient population

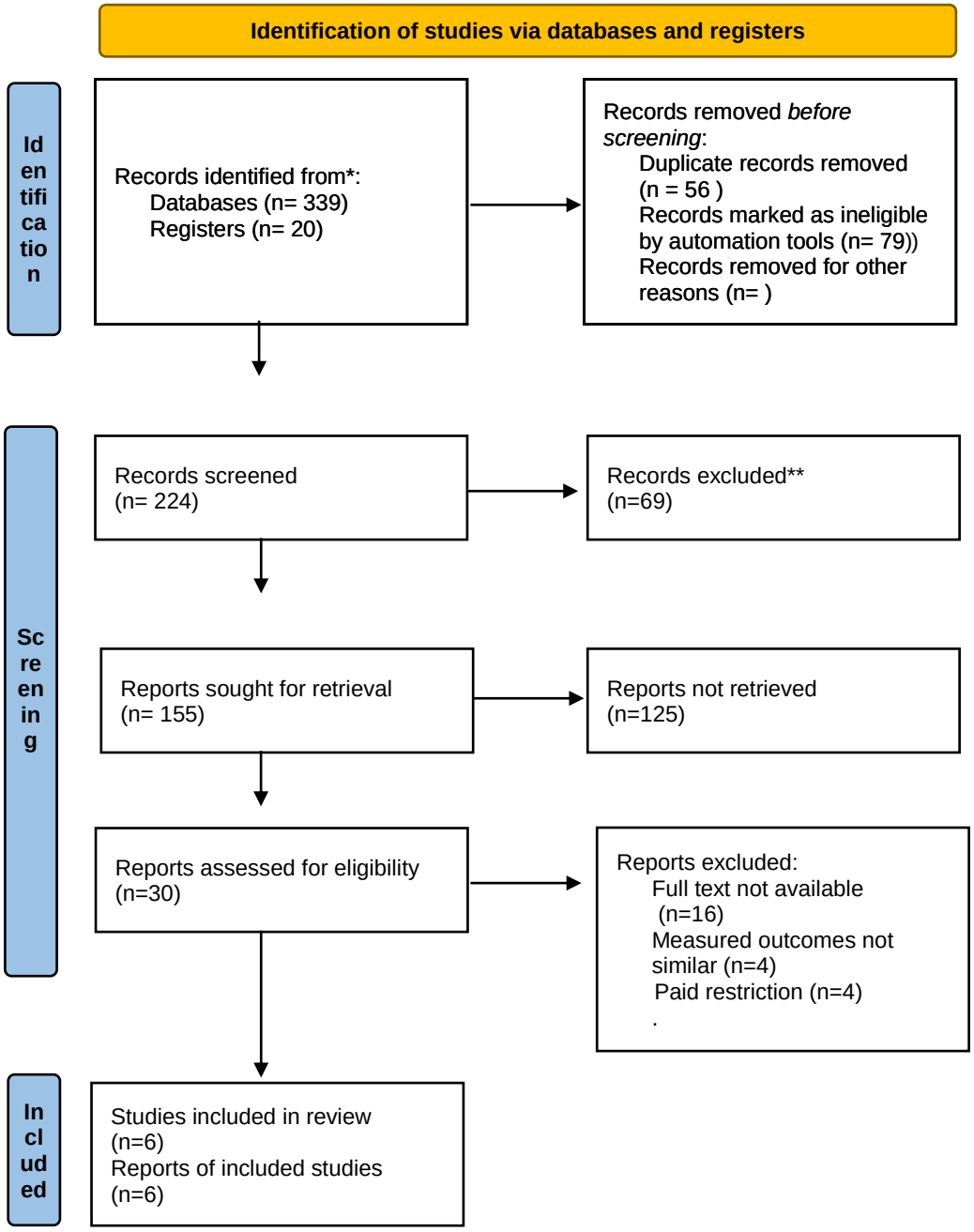

FIG 1 showing the PRISMA flow chart of this systematic review

Table 1: showing the basic characteristics of six eligible studies

Title	Author and date	Country of study	Full text	Study design	Control	Intervention	Number of participants	Median follow-up	Outcome	JADED Score	Included
Adjuvant Olaparib for-*/ Patients with BRCA1 or BRCA2-Mutated Breast Cancer	Tutt et al., 2021	USA	Yes	RCT	Placebo	Olaparib	1836	30 months	DFS, OS, Safety	3	**Included**

Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation	Robson et al., 2017	Sweden	Yes	RCT	Capecitabine/eribulin/Vinorelbin	Olaparib	302	14.5 months	PFS, ORR, OS	3	**Included**
Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes	Tung et al., 2020		Yes	Cohort		Olaparib	55	4.2 months	PFS, ORR	-	**Included**
Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial	Litton et al., 2020		Yes	RCT	Chemotherapy	Talazoparib	431	44.9 months	PFS, OS,	4	**Included**
Efficacy and safety of first-line veliparib and carboplatin-paclitaxel in patients with HER2-advanced germline BRCA+ breast cancer: Subgroup analysis of a randomised clinical trial	Arun et al., 2021	36 countries	Yes	RCT	Placebo	Veliparib	509	16.5 months	OS, PFS, ORR	4	**Included**
Talazoparib Versus Chemotherapy in Patients with HER2-negative Advanced Breast Cancer and a Germline BRCA1/2 Mutation Enrolled in Asian Countries:	Lee et al., 2021	Korea, Taiwan	Yes	RCT	Chemotherapy	Talazoparib	33		OS, PFS, ORR	3	**Included**

Exploratory Subgroup Analysis of the Phase III EMBRACA Trial	

RCT- Randomised controlled trials, PFS- Progression free survival, OS Overall survival, ORR-Objective response rate, DFS- Disease free survival

Table 2: Outcomes measured for each study

NCT Identifier	Author/year	Name of Study	Phase	Duration of treatment	Number of patients	PFS	ORR	OS	DFS	p-value
02000639	Robson et al., 2017	OlympiAD	3	8.2 months	302	7 months HR=0.58; 95% CI, 0.43-0.80)	-	45.7% HR=0.90; 95% CI, (0.63-1.29) P=0.57	-	<0.001
TBCRC 048	Tung et al., 2020	COHORT	2	4.2 months	55	2.6 months (90% CI, 8.4- 11.9)	33% (90% CI, 19%-51%)	-	-	-
01945775	Litton et al., 2020	EMBRACA	Open label-phase 3	36 months	431	8.6 months HR-0.54; 95%[CI], 0.41-0.71	62.6% odds ratio= 5.0; 95% CI, 2.9-8.8;	71% HR=0.848 (95% CI 0.670-1.073) P=0.17	-	<0.001
02163694	Arun et al., 2021	BROCADE3	3	-	509	16.6 months HR- 0.70, [95% CI] 0.54–0.89	79.7% odds ratio=0.71 95% CI (0.55–0.93)	36 months HR=0.92(95% [CI] 0.68-1.24 P-0.57)	-	0.004
02000622	Tutt et al., 2021	OlympiAD	2	36 months	1836	-	-	92% HR=0.68; 99% CI, (0.44-1.05) P=0.05	85.9% HR= 0.58; (99.5% CI, 0.41-0.82)	<0.001
-	Lee et al., 2021	ASIAN	3	-	33	9.0 months HR= 0.74 [95% CI] 0.22 to 2.44])	**62.5%** **[95% CI] 35.4 - 84.8**	20.7 months HR=1.41 [95% CI, 0.49 to 4.05])	-	< 0.001

RCT- Randomised controlled trials, PFS- Progression free survival, OS Overall survival, ORR-Objective response rate, DFS- Disease free survival,

DISCUSSION

Patients with advanced or metastatic TNBC who have a BRCA gene mutation may benefit from treatment with PARP inhibitors (15, 21, 22), this genetic mutation potentially runs in the family and is usually associated with development of breast cancer. The BRCA1/2 genes are essential for homologous recombination, and when they are altered, PARP inhibitors can stop non-homologous end joining by blocking PARP, causing synthetic death (5, 11, 18). This makes PARP inhibitors a potential therapy for breast cancer with a BRCA mutation (12). However, only breast cancer caused by a BRCA mutation has been approved for treatment with PARP inhibitors and all patients in relevant studies have had BRCA mutation (21, 22). Further research is still needed to determine the significance of a somatic BRCA mutation in the treatment of breast cancer. Following evidence of an improvement in progression-free survival, a better side-effect profile, and a better preservation of quality of life when compared to standard chemotherapy, olaparib as well as talazoparib have become approved as treatments of metastatic BC with BRCA1 or BRCA2 mutations (15, 17).

This review establishes PARPi effectiveness both as monotherapy or combination therapy in BRCA mutated TNBC. Additionally, it has been demonstrated that the effectiveness of PARPi in conjunction with carboplatin-paclitaxel increases the sensitivity of cancer cells to platinum-based chemotherapy. The treatment of choice for advanced breast cancer linked to the gBRCAm is platinum-based chemotherapy (18, 25). Patients with prior platinum exposure and a disease-free interval of at least 6 or 12 months as well as those without prior exposure to platinum have both experienced the effectiveness of PARPi (24, 25).

Overall, various studies indicate that the PARP inhibitors were generally well tolerated, with anaemia, fatigue, and nausea being the most frequent side effects. Additionally, there were instances of reduced neutrophil and white cell counts, however these only occurred in less than 1% of patients and were of grade 3 or higher. A tiny number of participants underwent blood transfusions, and some patients stopped taking the trial medicine as a result of negative side effects (15, 17, 18). However, it was determined that these severe adverse effects had nothing to do with the trial medications. Similarly, with regards to the average delivered-dose intensity, the median treatment duration differed between the different studies. The toxicity profiles of the PARP inhibitors and the control groups were different, and several medications caused more cases of anaemia, thrombocytopenia, nausea, and diarrhoea than the control groups. The trials didn't evaluate PARPi in diseases with platinum resistance (18, 24, 25). The ideal sequencing and therapy for BRCA mutation HER2-negative breast cancer require more study (27). The danger of severe hematologic toxicities is the greatest obstacle to employing PARP inhibitors as a treatment, but there is presently no mechanism to identify which individuals will be most affected (26). It is advised that all patients have their blood counts regularly checked as a result (27, 26). Some PARP inhibitors such as niraparib, are under advice according to directions of usage to only be administered to individuals who have previously recovered from hematologic toxicities brought on by chemotherapy (9, 27) as a means to prevent further adverse outcome.

Although, some studies report significant PARPi action in certain subsets of BC and other types of cancers such as prostate CA(32, 33), but according to this review, individuals who had mutations in specific HR-related genes (such as ATM or CHEK2) did not respond well to olaparib therapy(16).

In summary, this systematic review has limitations such as the diversity in study characteristics and the absence of adequately powered trials, which can introduce bias and limit the reliability of the results. Furthermore, to be able to safely assess the efficacy of an intervention, most studies reviewed were RCTs but one(16), which was a cohort study and only one arm of the cohort was considered which may not give an accurate representation of significance with the desired outcome measured.

CONCLUSION

Several clinical trials have demonstrated that PARP inhibitors can lead to objective responses, including complete and partial remissions, in a significant proportion of patients with BRCA mutated TNBC. In addition, these drugs have shown a favorable safety profile, with the majority of adverse effects being mild to moderate and manageable. Although there is a higher risk of myelosuppression associated with PARP inhibitor use, the results of the systematic review are promising. It is important to conduct long-term follow-ups for all patients receiving PARP inhibitors. This new treatment may be a major advancement for the subset of patients with BRCA mutations. However, while the efficacy and safety of PARP inhibitors in BRCA mutated TNBC is encouraging, there are still several areas of uncertainty that need to be addressed. For example, there is limited information on the long-term benefits of these drugs, as well as on their optimal use in combination with other treatments. In conclusion, the evidence to date suggests that PARP inhibitors are effective and well-tolerated in the management of BRCA mutated TNBC, offering a promising therapeutic option for patients with this disease. Further research is needed to better understand the optimal use and long-term benefits of these drugs in this patient population.

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