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"Efficacy and safety of oteseconazole in recurrent vulvovaginal candidiasis (RVVC) – A systematic review and meta-analysis"

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ABSTRACT

Background: Recurrent Vulvovaginal Candidiasis (RVVC) is defined as 3 or more episodes of symptomatic Vulvovaginal Candidiasis (VVC) within a year. Out of 75 % of women with VVC, this debilitating infection is experienced by 9 % of women. Although standard guidelines recommend oral and topical fluconazole as its treatment regimen, approval of another drug Oteseconazole has drawn the attention because of its better safety profile and lower recurrence rate by its use.

Aim: The purpose of our Meta-analysis is to evaluate the safety and efficacy of Oteseconazole (Vivjoa) (VT-1161) in the treatment of Recurrent Vulvovaginal Candidiasis (RVVC).

Methodology: Four databases namely PubMed, Google Scholar, Cochrane CENTRAL and Clinical Trial.gov were used from inception till June 2023. Studies that met the predefined inclusion criteria were statistically analyzed on RevMan (Version 5.4). A random effect model was used to pool the studies. A p value of less than 0.05 was considered significant and results were presented as Odds ratio with 95 % Confidence Intervals (CIs).

Result: The pooled analysis of our selected studies showed that Oteseconazole was associated with significantly reduced incidence of Recurrent Vulvovaginal Candidiasis (OR = 0.07; 95 % CI = 0.05–0.11; $p < 0.00001$, $I^2 = 0$ %) through week 48. Additionally, Vivjoa has also been shown by our analysis to reduce incidence of RVVC through week 24. (OR = 0.05; 95 % CI = 0.03–0.09; $p < 0.00001$, $I^2 = 0$ %) Furthermore, Oteseconazole was non-significantly associated with developing serious adverse effects during the treatment for Recurrent Vulvovaginal Candidiasis in comparison to the placebo (OR = 0.79; 95 % CI = 0.33–1.89; p = 0.60, I2 = 0 %).

Conclusion: The available evidence suggests Oteseconazole to be safer and more efficacious. However, limited patient population points towards the need of further large and dedicated trials for definitive conclusion.

1. Introduction

Vulvovaginal candidiasis (VVC) is defined as inflammation of epithelium of vagina and vulva. It is typically caused by Candidia albicans which is identified in 85–95 % of VVC infection [1,2]. However, multiple studies have reported non albicans Candida species

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as cause of VVC as well [3,4]. It is a debilitating infection, experienced by 75 % of women at least once in their lifetime [5]. Of those 75 %, 9 % of women with VVC may lead to development of Recurrent Vulvovaginal Candidiasis (RVVC) which is defined by Centre for Disease, Control and Prevention (CDC) as 3 or more episodes of symptomatic VVC within a year [5,6]. A large study by Denning et al. estimates the global yearly prevalence of RVVC to be 138 million women which is expected to rise to about 158 million women by 2030 [5].

The infectious Disease Society of American Guidelines recommends oral fluconazole for 10–14 days followed by 150 mg of fluconazole once a week for 6 months [7]. Another treatment regimen by U.S. CDC for RVCC is longer initial therapy of topical treatment for 7–14 days or oral dose of 100 mg, 150 mg and 200 mg of fluconazole on day 1, 4 and 7 respectively followed by antifungal maintenance period of oral fluconazole weekly for 6 months [6]. Intermittent use of topical azole agents is also under consideration if aforementioned options are not practicable [6]. Although these fluconazole maintenance suppressive therapies are effective in controlling RVCC, they are not curative and likely hazards (hepatotoxicity, torsade de pointes, seizures, leukopenia etc) associated with long term fluconazole use along with 50 % recurrence rate of VVC in less than 6 months of fluconazole maintenance therapy termination led to recent anticipated approval of safer and therapeutically more effective drug Oteseconazole (VT-1161) [8–10].

Many trials have been conducted to assess the safety and efficacy of Oteseconazole in treatment of RVCC, however, current data is based on heterogeneous population and no meta-analysis has been done to reinforce the results. Therefore the primary outcome of our meta-analysis is to study the efficacy and safety of Oteseconazole in treatment of RVVC.

2. Materials and Methodology

This review was not registered and no protocol was prepared. It followed the guideline set by Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). The PRISMA checklist is provided in Fig. S1. This was publicly available data, so neither patient consent nor institutional review board approval was necessary.

2.1. Data sources and search strategy

Four databases namely PubMed, Google Scholar, Cochrane CENTRAL and Clinical trial.gov were searched for studies showing the efficacy of Oteseconazole for recurrent vulvovaginal candidiasis from inception till JUNE 2023 without any language and time restriction. The medical subject headings (MESH) used for the search string are “Oteseconazole”, “VT-1161”, “Vivjoa”, “Recurrent vulvovaginal candidiasis.” The comprehensive search strategy used for all the databases is provided in Supplementary Table S1. Grey and white literature was searched. Variety of data sources were searched manually, namely bibliographies of the retrieved trials, editorials, conference proceedings for indexed abstracts, meta-analysis, and systematic reviews to ascertain eligible studies.

2.2. Study selection

Following were the eligibility criteria established for the selected studies.

a The study design including Randomized control trials (RCT) and observational studies i.e. cross-sectional, cohort and case-control were integrated based on the eligibility criteria.
b The targeted population was the patients with the history of recurrent vulvovaginal candidiasis.
c The outcome was the effect of Oteseconazole and placebo as an intervention and control on the recurrent vulvovaginal candidiasis respectively.
d All studies which didn’t meet the pre-specified criteria or their study designs were classified as case reports, meta-analyses, or not released as published reports, studies with irrelevant outcomes, and irrelevant populations were excluded.

All the articles were retrieved from the systematic search were compiled and exported to EndNote Reference library software (X7 v17.0.0.7072) where duplicates were assessed and removed. Relevant articles were evaluated by two independent reviewers (TS and PRD) based on the pre-defined eligibility criteria. No study had missing summary statistics and we didn’t have to convert data of any study. Any further discrepancies were resolved and cross checked by third investigator.

2.3. Data extraction and quality assessment

Baseline characteristics and Outcome data were extracted on the basis of pre-defined criteria into the Microsoft Excel Sheet. Summary events and total were extracted and used for the analysis of the outcome. Cochrane Risk of Bias tool (CRBT) was used for the quality assessment of the included RCTs [11]. Data Extraction and Quality assessment were conducted by two independent reviewers (KAK and FE) and any discrepancies were solved by group discussion till consensus. We also assessed certainty of the studies by assessing them for risk of bias.

2.4. Statistical analysis

RevMan (Version 5.4; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to conduct all statistical analyses. The outcomes of interest was extracted in the form of raw data containing events and total, which was calculated

into odd ratios (OR) and 95 % CI and were pooled using inverse-variance weighted random-effects model. Pooled data analysis was visually evaluated through forest plots. Higgins I2 statistics were used to assess heterogeneity across studies, with values ranging from 25 % to 50 % being mild heterogeneity, 50 %–75 % being moderate heterogeneity, and >75 % is considered severe heterogeneity [12] In all cases, a p-value of <0.05 was considered significant. Heterogeneity was found to be zero so subgroup analysis and meta regression have not been performed. Sensitivity analysis was done to assess the robustness of synthesized results. Funnel plots were not made and Begg's and Egger's tests were not performed for the assessment of publication bias as our meta-analysis didn't contain required number of studies needed to perform these tests.

3. Results

3.1. Literature search

Four electronic databases namely PubMed, Google Scholar, Cochrane Central and Clinical gov.trial were used for the literature search. This yielded 304 citations and after undergoing the process of removal of duplicates, screening based on title and abstract and assessment based on eligibility criteria, 4 randomized clinical trials were obtained for the meta-analysis. The complete descriptive literature search has been outlined in the PRISMA flowchart in Fig. S1.

3.2. Study characteristics and patients' characteristics

Study characteristics and patient's baseline characteristics and outcome information have been summarized in Table S2 and Outcome table in supplementary files respectively. Our analysis included a total of 1106 participants, with 751 participants in the intervention group and 335 participants in the control group. The age of patients varied from 34 to 35 years with a mean of 34.2 years.

3.3. Quality assessments and publication bias

RCTs were assessed for the quality assessment on Cochrane Risk of Bias tool (CRBT). All the included studies had low risk of bias which is depicted in risk of bias summary Fig. S2.

3.4. Outcome analysis

All the 4 included studies reported the data on the efficacy of the Oteseconazole for recurrent vulvovaginal candidiasis. There were total of 1106 participants, amongst which 751 patients were in the intervention group and 335 in the control group. The pooled analysis showed that Oteseconazole was associated with significantly reduced incidence of recurrent vulvovaginal candidiasis through week 48 (OR = 0.07; 95 % CI = 0.05–0.11; p < 0.00001, I^2 = 0 %) (Fig. 1).

The pooled analysis of Oteseconazole as intervention through week 24 also demonstrated it to be statistically significant in reducing recurrence of RVVC than placebo. (OR = 0.05; 95 % CI = 0.03–0.09; p < 0.00001, I^2 = 0 %) (Fig. 2).

The forest plot was also formed for the evaluation of the serious adverse effects that emerged during the treatment with Oteseconazole and placebo for recurrent vulvovaginal candidiasis. It showed that Oteseconazole was non-significantly associated with developing serious adverse effects during the treatment for recurrent vulvovaginal candidiasis in comparison to the placebo (OR = 0.79; 95 % CI = 0.33–1.89; p = 0.60, I2 = 0 %). Fig. 3.

Heterogeneity was found to be zero so subgroup analysis and meta regression have not been performed.

3.5. Qualitative analysis

Brand SR et al.: A phase 2 randomized double-blind placebo-controlled trial conducted by brand SR et al. shows a decline in the recurrence rate of RVVC with the use of oteseconazole compared to placebo. The duration of the study was from February 2015 to November 2016. Patients with a documented history of RVVC, defined as three or more episodes of acute VVC in the past 12 months,

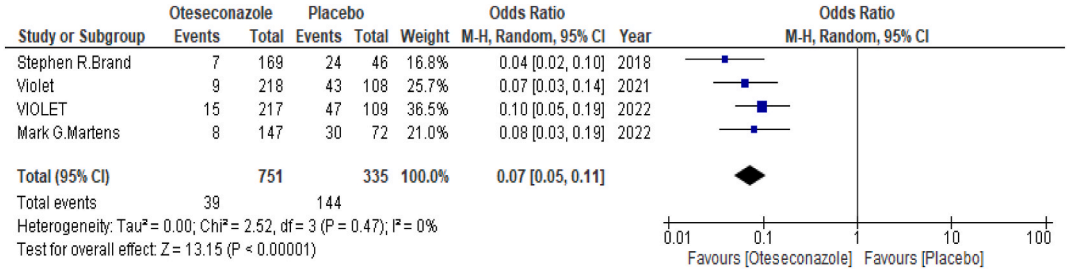

Fig. 1. Forest plot comparing the efficacy of using Oteseconazole as an intervention vs. placebo as a control for the occurrence of recurrent vulvovaginal candidiasis through week 48.

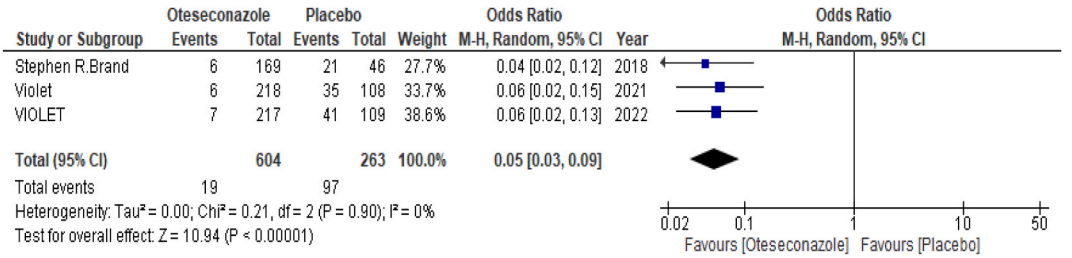

Fig. 2. Forest plot comparing the efficacy of using Oteseconazole as an intervention vs. placebo as a control for the occurrence of recurrent vulvovaginal candidiasis through week 24.

Fig. 3. forest plot comparing the serious adverse effects of using oteseconazole as an intervention vs. placebo as a control during the treatment of recurrent vulvovaginal candidiasis.

including the episode at the screening visit, were included. This trial included 2 phases, an induction phase with 3 sequential doses of fluconazole for the treatment of acute VVC episodes succeeded by a maintenance phase in which patients were randomized to receive either one of the 5 treatment arms (4 treatment arms included VT-116 vs. 1 treatment arm of placebo). All treatment arms of VT-1161 displayed statistical significance in reducing recurrence of RVVC over placebo, Cochran-Mantel-Haenszel test with stratification was used to compare differences in treatment between each VT-1161 group and placebo.

Violet 2021: This is a phase 3 randomized controlled double-blind trial which enrolled patients with a history of RVCC that was presented with a clinical diagnosis of acute VVC. This trial, with a duration from October 2018 to October 2020 consisted of an induction phase followed by a maintenance phase in which patients were randomized to receive either Oteseconazole or Placebo in a 2:1 ratio. Participants received a loading dose of 150 mg of oteseconazole once daily for a week, followed by a maintenance dose of 150 mg once weekly starting from weeks 2–12 of the study. The chi-squared method was used to perform statistical analysis which proved Oteseconazole to be superior in reducing incidence of RVVC than placebo.

Violet 2022: This phase 3 randomized controlled trial consisted of a 2-week induction phase in which patients were given fluconazole backed by a maintenance phase in which patients were randomized to receive either Oteseconazole or Placebo with period 2 as a baseline period. The duration of the trial was from October 2018 to October 2020. The Logrank method of analysis demonstrated Oteseconazole to be statistically significant in the prevention of RVVC than placebo.

Mark G. Marten et al.: A phase 3 multicenter, randomized, double-blind, placebo-controlled parallel group trial had a two-week induction phase in which subjects were randomized in a 2:1 ratio to receive either Oteseconazole or Fluconazole/placebo. Following this, participants were randomly assigned to receive Oteseconazole vs. Placebo. The duration of this trial was 50 weeks. Efficacy analysis of the primary endpoint was performed using a chi-square test, which showed Oteseconazole to be superior to placebo in mitigating the frequency of RVVC.

3.6. Dose effect relationship

Brand et al - In the ITT population, the proportion of participants with one or more positive mycologic cultures during 48 weeks was less in the VT-1161 arms [6 subjects (14.3 %) in the 150 mg/12-week treatment group; 10 subjects (23.3 %) in the 150 mg/24-week treatment group; 7 subjects (16.3 %) in the 300 mg/12-week treatment group; and 3 subjects (7.3 %) in the 300 mg/24-week treatment group) in comparison with 35 subjects (76.1 %) in the placebo group].

Mark G. Marten et al. - During the 2-week induction phase, Oteseconazole was given orally at a dose of 600 mg on the first day and 450 mg on the second day, which was found to be non-inferior to fluconazole in treating acute VVC. In the maintenance phase, administering a weekly dose of 150 mg of oteseconazole for 11 weeks was better than a placebo in preventing the recurrence of acute VVC episodes for individuals with a history of RVVC.

Violet 2021- During the maintenance phase, the proportion of the subjects with one or more positive cultures for Candida species was reported for the timeframe of 48 weeks. It showed that 60 out of 218 patients in the interventional arm had positive culture as compared to 91 patients out of 108 in the control arm. Therefore, Oteseconazole is better than placebo in preventing the recurrence of acute VVC episodes.

Violet 2022- During the maintenance phase of the ITT population, the effectiveness of Oteseconazole in preventing RVVC was evaluated by measuring the proportion of participants who had one or more positive cultures for Candida species within 48 weeks. The results revealed that out of the 217 patients in the intervention group, only 15 had positive cultures for Candida species, compared to 45 patients out of 109 in the control group. These findings suggest that Oteseconazole is a potent drug in preventing RVVC.

4. Discussion

In this meta-analysis comprising 1106 vulvovaginal candidiasis patients, we demonstrated statistically significant efficacy and safety of Otesecanazole, in the prevention of one of the most abrasive women health issues, recurrent vulvovaginal candidiasis. This is particularly noteworthy and mentionable because this is the first meta-analysis that has reported this finding by pooling the results of 4 available clinical trials. (Figure forest plot).

Current treatment guideline for RVVC has been presented in tables S3, S4 and S5given below [6]. At present, the first line maintenance regimen for RVCC, as recommended by Centers of Disease Control and Prevention is Oral Fluconazole weekly for 6 months. However, it comes with some adverse effects and liabilities limiting chronic dosing such as liver toxicity, drug-to-drug interactions and increased risks for miscarriage and birth defects when used while pregnancy [6,8]. In contrast to that, Otesecanazole significantly reduces the risk of recurrent vulvovaginal candidiasis as shown by our analysis (OR = 0.06; 95 % CI = 0.04–0.09; $p < 0.00001$, I2 = 0 %) with no reported significant adverse effects. According to CL-011 and CL-012, the oral intake of Oteseconazole through week 48 was highly efficacious (hazard ratio [95 % confidence interval], 0.11 [0.06 to 0.21] for CL-011 and 0.08 [0.04 to 0.17] for CL-012; $P < 0.001$) having strong effectiveness against fluconazole-resistant C. albicans and C. glabrata species, in avoiding the recurrence in VVC participants with a history of RVVC [13]. The main reason this drug is more potent, efficacious and superior to fluconazole is because of its activity against fluconazole-resistant species that cause RVVC that has very few viable options for treatment. Similarly, in phase 3 clinical trial, both drugs were compared in terms of efficacy and safety to treat RVVC and acute VVC and the most interesting finding is that only 5.1 % of participants in the Oteseconazole group had at least one culture validated for an acute VVC episode, compared to 42.2 % of those in the fluconazole group (P 0.001) [14]. Oteseconazole was also statistically superior in prevention of recurrent VVC episodes with efficacy findings in favor of Oteseconazole during maintenance phase, proportion of participants with more than 1 positive cultures for candida during maintenance phase and time of recurrence of first culture verified acute VVC [14].

The prior analysis by Rosa et al. demonstrated the effectiveness of fluconazole in suppressing symptomatic episodes of VVC rather than eradication [15]. In the 10–20 % of women infected with non-albicans candida species, RVVC demonstrated high resistance to the azole group of antifungal agents. Furthermore, long-term use of fluconazole decreases the rate of clinical recurrence in RVVC patients, however, a long-term cure remains difficult to attain [15]. In addition, other azoles possess an imidazole or triazole moiety that can inhibit human cytochrome P450 (CYP) as well. On the other hand, Oteseconazole is highly selective as it contains tetrazole moiety that doesn't inhibit human CYP51, thus making it a better regimen to administer [16].

Although, Oteseconazole has been shown to have potent activity against RVVC, however, some limitations should be considered when interpreting our findings. Oteseconazole is contraindicated in pregnant women and females of reproductive potential as it can cause fetal harm. It is also contraindicated in lactating women, although, there is no data on the presence of Oteseconazole in human or animal milk or data on the effects of Oteseconazole on milk production. Furthermore there were no reported adverse effects in breastfed infants following maternal exposure to Oteseconazole during lactation; however, given the limited duration of follow-up of the Oteseconazole-exposed infants during the post-natal period, no conclusions can be drawn from these data [17]. Also, the treatment cessation if done within 6 months reported relapses indicating prolonged administration therapy [18]. Table S6 given below demonstrates the toxicity that arises due to long term use of oteseconazole as well as fluconazole [10,19].

Oteseconazole, if available with effective cost and unchanged AE profiles, could become a phenomenal treatment consideration for women with RVCC with its positive safety profile and amazing efficacy as existing needs are not being fulfilled by oral and topical azole drugs accessible.

4.1. Implications for practice and/or policy

In our world, where many women have to go through bothersome recurrent vulvovaginal candidiasis, our study highlighted a safer, more efficacious and less hazardous drug regimen Oteseconazole as a potential treatment option and showed its statistical significance in reducing the incidence of RVVC.

5. Conclusion

In conclusion, Oteseconazole is significantly efficacious and safer drug used in treatment and prevention of Recurrent Vulvovaginal Candidiasis (RVVC).

Data availability statement

Data included in article/supplementary material/referenced in article.

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CRediT authorship contribution statement

Tasmiyah Siddiqui: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Kanwal Ashok Kumar:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Amna Iqbal:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Payal Rani Doultani:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Tayyaba Ashraf:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Farea Eqbal:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Samrah Inam Siddiqui:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20495.

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