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Oteseconazole - An advance in the treatment of Recurrent Vulvovaginal Candidiasis?

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Abstract

Recurrent vulvovaginal candidiasis (RVVC), a major therapeutic problem worldwide, defies ready cure and serves as a major ongoing challenge with high rates of symptomatic recurrence. Past treatment has been limited to maintenance prophylactic fluconazole regimens which frequently fail to meet the needs of patients and is further challenged by increased rates of fluconazole resistance in C. albicans and non-albicans Candida species isolates. Oteseconazole provides enhanced in vitro potency, broader spectrum antifungal activity and a prolonged half-life offering enhanced therapeutic outcome, however administrative restrictions on its clinical indications will result in significant limitations in short term future use. Its role in clinical practice is discussed.

Background

Vulvovaginal Candidiasis (VVC) affects women across all strata of society and better therapeutic options are needed [1]. Currently available antifungal agents, both topical and oral, although widely used in a variety of strategies, continue to fail to meet the therapeutic needs of women suffering from lower genital tract fungal infection. A number of antifungal drug are already available, many with over the counter accessibility, are highly effective in relieving acute vulvovaginal symptoms. However current antifungal treatment, which is largely azole drug class dependent, fails to provide an overall satisfactory solution for recurrent VVC (RVVC) [2-5]. Prophylactic fluconazole therapy, usually prescribed as a long term weekly regimen is rarely curative and has numerous limitations including cost, compliance issues, drug allergy and intolerance [6-8]. Most importantly, cessation of prophylactic therapy is followed by high rates of VVC recurrence once treatment is stopped and in spite of a variety of drug strategies in widespread use [2,3,6]. To these deficiencies must be added a new growing problem of increased frequency of reports worldwide of fluconazole and other azole drug resistant Candida species responsible for acute VVC and especially RVVC [3, 9, 10, 11].

Azole resistance has long been known, but previously was almost entirely associated with non-albicans Candida species including C. glabrata, C. krusei, C. parapsilosis etc., and non-Candida yeast pathogen Saccharomyces cerevisiae [3]. However not traditionally recognized as a resistant species is C. albicans by far the dominant cause of VVC and RVVC [9]. Several investigators have now reported an increased and growing frequency of fluconazole resistant C. albicans vaginal isolates obtained from women with clinically refractory VVC and breakthrough episodes of yeast vaginitis in women with RVVC [9-11]. Sounding the alarm, clinicians have searched for antifungal agents active against fluconazole resistant Candida isolates of all species [12]. Two new antifungals were FDA approved for VVC recently with impressive in vitro clinical and animal model data [13,14]. There emerged the presumption that a solution was now at hand and available to meet the growing needs of women with acute sporadic and RVVC. These antifungal agents Ibrexafungerp and Oteseconazole are now available and have been reviewed by several investigators, with new efficacy data emerging on a monthly basis. The purpose of this review is to provide an updated commentary on oteseconazole and its use for VVC and RVVC. **Table I** lists the aspirational characteristics of any new antifungal drug introduced for all forms of vulvovaginal candidiasis.

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Table 1: Aspirational goals of new antifungal drugs introduced for VVC.

• Safety in pregnancy
• Safe in patients allergic to fluconazole and topical azole agents
• Safe and well tolerated with few adverse reactions (few drug interactions) or contraindications (e.g. prolonged QT interval)
• Oral preference
• Single day/dose regimen
• Efficacy in acute symptomatic VVC
• Effective long term prophylaxis (>90%) in RVVC
• Post therapy efficacy in reducing VVC recurrence, especially in women with RVVC
• Effective both clinical and mycologic against yeast species resistant to fluconazole (intrinsic and acquired)
• Inexpensive

Preclinical Pharmacology

Oteseconazole (VT-1161), a tetrazole, inhibits lanosterol 14α-demethylase (ERG11, CYP51) has been designed to have greater specificity for fungal CYP51 enzyme, with the triazole iron-binding group replaced with a tetrazole and with modification of the portion of the molecule recognized by amino acids of the substrate-binding site within CYP51 [15,16]. As such oteseconazole is reported to have a greater affinity for fungal CYP51 compared to human enzymes (~2000-fold)[16,17]. Oteseconazole mechanisms of activity is the same as triazole but with greater selectivity for fungal enzymes and potentially fewer adverse effects and drug-drug interactions.

Oteseconazole is broadly active against Candida species, including fluconazole resistant isolates causing fungal vaginitis [17-19]. As such, resistance can occur by the same mechanisms that cause resistance to triazoles, but several additional mechanisms have already been reported including ERGT3 gene mutation, ERG11 enzyme amino-acid substitution and as anticipated over-expression of the ATP-binding cassette transporter genes CDR1 and MDR1 [19,20]. Zinc cluster transcription factors affecting ergosterol biosynthesis and efflux pumps are now also reported, accordingly resistance mechanisms are possible in the future [15].

In vitro studies indicate that MIC's for oteseconazole for C. albicans were significantly lower compared to fluconazole [17]. This enhanced potency is similarly evident against non-albicans Candida species including C. glabrata [21,22]. Oteseconazole MIC's were approximately 6 fold lower than fluconazole MIC's against C. glabrata [21]. Similarly enhanced in vivo activity compared to fluconazole was observed in the animal model of vaginal candidiasis [23].

Pharmacokinetics and metabolism

Following oral administration approximately 76% of oteseconazole is absorbed. Plasma concentration increased in a dose dependent manner. Approximately 5-10 hours was needed for oteseconazole to reach peak plasma concentration, with 45% increase in Cmax following oteseconazole intake with a high fat meal compared to fasting state [24].

Oteseconazole is highly bound to plasma protein (99.5%-99.7%) with a volume of distribution of 423 liters. Of note, in animal studies oteseconazole achieved vaginal concentration 2-fold higher than plasma levels following oral ingestion [23]. Oteseconazole was shown to have a low rate of metabolism with a median terminal half-life in humans of 138 days, ensuring good tissue drug exposure. The long half-life leading to sustained plasma levels and drug exposure has also been observed in animals [15]. The drug is mainly excreted in feces and urine (56% and 26% respectively) suggesting potential therapeutic use for candiduria.

Safety and Drug Interactions

In clinical trials, oteseconazole was well tolerated in all dosing groups [25-28]. The most common adverse events occurring were headaches (7.4%) and nausea (3.6%) [25]. No serious adverse events leading to drug discontinuation were reported. Unlike fluconazole, oteseconazole does not prolong the QT interval to a clinically relevant extent.

Oteseconazole inhibits Breast Cancer Resistance Protein (BCRP) and increased the peak serum concentration (Cmax) and overall exposure of the BCRP substrate rosuvastatin. If oteseconazole is used with a BCRP substrate, then a reduction in the dose of the substrate may be necessary. By design oteseconazole has a lower affinity for human CYP enzyme than other members of the azole class. Accordingly is a only weak inhibitor of CYP2C9, 2C19 and 3A4 in vitro [17]. Coadministration of oteseconazole was not found to have a clinically significant effect on the pharmacokinetics of the CYP3A4 substrates nor ethindrone, ethinyl estradiol and midazolam. These data support the conclusion that oteseconazole has greater selectivity for fungal CYP51 compared to human CYP450 enzymes [15]. As such oteseconazole is a much weaker inhibitor of CYP substrates than fluconazole and does not increase serum concentrations of drugs metabolized by these enzymes [29].

Most importantly, in an animal study ocular abnormalities were observed in the offspring of certain strains of rats given oteseconazole at doses approximately 3.5 times the dose given to humans [30]. As such the drug is contraindicated in pregnancy and lactating women, joining both fluconazole and ibrexafungerp in this major limitation of its use. In addition because of its prolonged half-life and persistence in tissues for many months, oteseconazole is contraindicated for use in females of reproductive potential including those using effective contraception and available for use only in post-menopausal women and following hysterectomy or tubal ligation.

Clinical Studies

A Phase 2 proof-of-concept study of efficacy, tolerability and PK was conducted in patients with moderate to severe acute VVC [26]. Sixty-five, healthy nonpregnant females with acute symptomatic VVC were enrolled in this dose-ranging study. Dosage of oteseconazole were 300mg daily for 3 days, 600mg daily for 3 day, or 600mg twice daily for 3 days and compared to sin-

gle dose fluconazole 150mg in which therapeutic cure was determined at day 28, but follow up was continued for 5 months. In the Intent-To-Treat (ITT) population, the low, mid, and high dose oteseconazole groups achieved therapeutic cure at rates of 66.3%, 75.0% and 78.6% in comparison to 66.7% in the fluconazole group, with no statistically significance at day 28; so establishing the early equivalent efficacy of oteseconazole for acute VVC. More importantly in this early study was the finding of significantly reduced VVC symptom recurrence over the long term with all participants who received oteseconazole demonstrating mycologic cure at 3 and 6 months. In contrast half the participants receiving single dose fluconazole showed mycologic recurrence by 6 months. Unfortunately higher doses of fluconazole were not used in this comparison. A basis was now established to allow oteseconazole to be studied in woman with either acute or RVVC.

Accordingly a phase 2B multicenter, randomized, double blind, placebo-controlled, dose-ranging study of treatment for RVVC with clinical diagnosis of symptomatic acute VVC and history of RVVC was initiated [25]. In the ITT population, seven of 169 (4.1%) participants in the oteseconazole treatment groups had a culture verified episode of VVC versus 24 of 46 (52.2%) participants in the placebo group ($p < 0.0001$) accompanied by dramatically reduced mycologic recurrence in the oteseconazole groups. Once more the study showed that oteseconazole was effective in treating acute and RVVC with a sustained therapeutic effect [25].

The stage was now set for large phase 3, randomized placebo controlled studies (VIOLET); CL-011 and CL-012 [27]. In these trials, C. albicans represented 87% of the organisms isolated from the vaginal swabs followed by C. glabrata (8%). Other organisms identified included C. parapsilosis, C. tropicalis, C krusei, C. dubliniensis, C. kefyr and S. cerevisiae. Among 656 women (326 in CL-011 and 320 in CL-012), the induction regimen in participants with acute symptomatic VVC consisted of one dose of fluconazole 150mg every 72 hours and those with resolved signs and symptoms were then randomly assigned to a treatment group in a ratio of 2:1 to receive 150mg of oteseconazole daily for 7 days, followed by 150mg of oteseconazole weekly for 11 weeks or matching placebo for 12 weeks (maintenance phase).

Most importantly, participants in both groups were then followed after treatment was stopped for an additional 36 weeks: for a total of 48 weeks. The average percentage of participants with one or more RVVC episodes through week 48 was 6.7% (range 6.5 to 7.4%) in CL-001 and 3.9% (3.7 to 4.6%) in CL-012, the oteseconazole groups versus 42.8% (41.3 to 45.0%) and 39.4% (38.0 to 42.1%) in the corresponding placebo groups ($p<0.001$). In addition among oteseconazole treated participants who experienced a recurrence of VVC (n =22), the mean time to recurrence was 45.7 and 47.2 weeks versus 27.8 and 33.1 weeks in placebo treated participants (n=84), respectively (hazard 0.11 for CL-011 and 0.08 for CL-012, $p<0.001$). Data analysis included several imputations including participants lost to follow up as being considered failures, however the increased time to VVC recurrence rate for oteseconazole remained statistically significant [31].

Side effect percentage was similar between the treatment groups in both trials, with no drug-related or treatment attributed serious adverse effects, including no adverse obstetrical outcomes, liver function or QT interval abnormalities.

An additional phase 3 trial followed (ultraVIOLET) in women with RVVC with acute symptomatic VVC at enrollment, in which the previously used fluconazole induction therapy was replaced by oteseconazole 600mg (4 tablets at 150mg) single dose and 450mg (3 tablets 150mg) on day two, at the time that participants in the placebo arm received three doses of fluconazole [28]. In both arms prophylactic maintenance antifungal therapy was administered once weekly for 11 weekly, either oteseconazole 150mg or placebo. The primary efficacy outcome measure was the proportion of participants with ≥1 culture-verified acute VVC episodes through week 50. Only 5.1% of the oteseconazole treated group had ≥1 culture verified acute VVC episode versus 42.2% in the group receiving placebo ($p<0.001$). Once more significance was retained despite various analyses correcting for imputations [25].

Although not the primary goal of the ultraVIOLET trial, oteseconazole use in the induction phase prior to initiation of maintenance oteseconazole, demonstrated efficacy as treatment of acute VVC (93.2%) compared to fluconazole (95.8%) when evaluated on day 14. Similarly no significant difference in side effects were reported. Oteseconazole has not received FDA approval for use in acute VVC in all-comers and the dose used in ultraVIOLET study may not be the recommended dose especially in women with acute uncomplicated VVC.

Although data are not as yet published, an extension study occurred in women with RVVC who had participated in the VIOLET study and followed for 48 weeks and remained asymptomatic without VVC recurrence, who were then followed for a further 48 weeks i.e. almost 2 years. The results were presented at a national scientific meeting. Of the 435 oteseconazole-treated participants, 71 were enrolled and 60/71 (88%) completed 96 weeks without a recurrent VVC episode i.e. providing long-term prevention of disease recurrence [32].

Indications

Oteseconazole is FDA approved for prevention of vaginitis recurrence in women with RVVC. As such it will soon be joined by Ibrexafungerp for the same indication. Both offer a solution for women, not adequately controlled by weekly fluconazole, but not a large number infected with C. albicans. The use these agents represent a major advantage and benefit for women with RVVC in whom limitations are clearly apparent, notably women allergic and intolerant to fluconazole and in particular those women with RVVC caused by a fluconazole-resistant Candida or non-Candida isolate. All three oral antifungal agents are contraindicated in pregnancy, leaving gravid women without an oral antifungal agent to prevent and treat VVC in pregnancy. Unfortunately the relative merits of both new antifungals have not been adequately measured because of lack of in vivo efficacy comparisons with fluconazole in clinical trials or by comparison with each other. None of these important requirements are demanded by the Food and Drug Administration (US). So once more this leaves only a markedly reduced and limited non-pregnant population of women with RVVC in need of alternative to or improvement of fluconazole viz women allergic or intolerant of fluconazole and now failing with fluconazole due to in vitro and in vivo resistance. The extended FDA restriction in use limiting use of oteseconazole to only woman without reproductive capacity further reduces the vulnerable population in need by approximately 70-80%. In addition another challenge to oteseconazole, now available commercially, is expense. This is what remains for a new highly potent agent, well tolerated by women in large randomized control trials and demonstrating superior in vitro and in vivo activity against azole resistant vaginal patho-

gens especially C. glabrata [27]. What is frustrating to clinicians is that recurrence rates of VVC in preliminary non-comparative studies appear impressively reduced for vastly extended periods following cessation of prophylactic antifungal therapy, likely related to the prolonged half-life of oteseconazole with persistent virginal tissue presence preventing yeast recolonization [27, 32].

Although not formally approved, there is evidence from phase 2 and 3 studies that single day oteseconazole is at least as effective short term for acute VVC as multi-dose fluconazole in the absence of a history of RVVC [26,28]. As with any new antifungal available for VVC, the optimal dose, regimen and treatment regimen has yet to be determined or recommended and will likely emerge with time and experience with clinical use. This incomplete information applies particularly to the multiple Candida species serving as vaginal pathogens with a particular challenge posed by C. glabrata.

Conclusion

Oteseconazole has not been compared to oral weekly fluconazole, the prevailing treatment standard worldwide used for many years as the optimal maintenance treatment for RVVC. Compared to fluconazole, oteseconazole offers shorter duration of treatment, fewer drug interactions and greater in vitro and in vivo activity against almost all species of Candida and is critically useful when clinical and in vitro resistance is evident. It is however more expensive and contraindicated in pregnant, lactating and women of reproductive capacity.

Disclosures

No funding or support was available for preparation of this manuscript.

Conflicts of Interest

J.D. Sobel MD has served as a consultant on the scientific advisory committee for Mycovia Pharmaceuticals Ltd

J.D. Sobel MD has served as a consultant on the scientific advisory committee for Scynexis Pharmaceuticals Ltd.

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