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CLINICAL ARTICLE

A multicenter, double-blind, randomized, placebo-controlled study of rifaximin for the treatment of bacterial vaginosis

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ABSTRACT

Objective: To compare efficacy and tolerability between different regimens of rifaximin vaginal tablets and a placebo for treatment of bacterial vaginosis. *Methods:* In a prospective study carried out at 13 sites in 3 European countries between August 2009 and October 2010, White, non-pregnant, premenopausal women with bacterial vaginosis were randomly assigned to receive rifaximin at 100 mg for 5 days (100 mg/5 days), 25 mg/5 days, or 100 mg/2 days, or placebo. Women were assessed at 7–10 and 28–35 days. Diagnosis and cure were based on Amsel criteria and Nugent score. Fisher exact test was used to compare cure rates. *Results:* Among 114 women recruited, 103 were evaluable for drug efficacy. Therapeutic cure rate at first follow-up was higher in the rifaximin 25 mg/5 days (48%, $P=0.04$), 100 mg/2 days (36.0%), and 100 mg/5 days (25.9%) groups than in the placebo group (19.0%). At second follow-up, therapeutic cure rate was 28.0%, 14.8%, and 4.0% in the respective groups versus 7.7% in the placebo group. No difference in adverse events was observed. *Conclusion:* Rifaximin at 25 mg/5 days showed better therapeutic cure rates and maintenance of therapeutic cure after 1 month versus placebo. All treatment regimens were well tolerated.
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1. Introduction

Bacterial vaginosis, one of the most frequent vaginal infections [1,2], is an ecologic disorder of the vaginal microbiota, characterized by a massive overgrowth of mixed commensal anaerobic and/or microaerophilic flora replacing protective lactobacilli [3–5]. Although perceived as a mild medical problem, bacterial vaginosis is associated with an awful disease burden and with adverse obstetric and gynecologic outcomes [6–9].

Current standard antibiotic therapies—that is, oral or vaginal metronidazole or clindamycin—have similar clinical cure rates of 60%–90% at 1 month [10]; however, relief is often short-lived, and recurrence occurs in 15%–30% of women within 1–3 months and 50%–70% of women within 6–12 months [11]. Moreover, these drugs are systemically absorbed and are not infrequently associated with adverse effects such as nausea, abdominal cramping, unpleasant taste [12], and vulvovaginal candidiasis [13]. Severe pseudomembranous colitis has also been reported [14].

Rifaximin (Alfa Wassermann, Bologna, Italy)—a virtually non-absorbed antibiotic derivative of rifamycin with broad-spectrum antibacterial activity covering Gram-positive, Gram-negative, aerobic, and anaerobic bacteria—has been used to treat gastrointestinal infections as an oral formulation and, being negligibly absorbed, presents a good safety profile [15]. Because rifaximin is also active against many organisms responsible for genital infections, local use of this antibiotic for the treatment of bacterial vaginosis has been suggested [16].

The aim of the VARIANT 1 (vaginosis rifaximin treatment) study was to evaluate efficacy and tolerability of 2 doses and 2 treatment durations (100 mg for 5 days, 25 mg for 5 days, and 100 mg for 2 days) of rifaximin vaginal tablets versus a placebo for the treatment of bacterial vaginosis.

2. Materials and methods

In an early Phase 2, multicentric, randomized, double-blind, placebo-controlled study conducted at 13 study sites in 3 European countries, women affected with bacterial vaginitis were enrolled between August 14, 2009, and October 19, 2010, in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the independent ethics committees

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of each study center, and all participants provided written informed consent before being enrolled in the study.

White, non-pregnant, premenopausal women, aged 18–50 years, were eligible for the study. In accordance with the US Food and Drug Administration (FDA) definition, bacterial vaginosis was diagnosed on the basis of the combined presence of at least 3 out of 4 Amsel criteria [17] and a Gram stain Nugent score of 4 or higher [18]. Participating women were required to abstain from intercourse during the 5-day treatment period and for 3 days before the follow-up visits, to avoid the use of intravaginal products, including douches, sprays, tampons, spermicides, gels, foams and diaphragms, and to adopt an adequate contraceptive method during the study.

Women were excluded from the study if they were pregnant or breast-feeding, anticipated menses at screening or follow-up visits, or had received systemic or vaginal antimicrobial therapy in the 2 weeks before the study. Additional exclusion criteria were dysplastic findings on a cervical Papanicolaou smear or having had cervical cryo-, laser- or conization therapy in the past 3 months; clinical evidence of genital herpes; any chronic or debilitating disease; history of drug or alcohol abuse; mental illness; known hypersensitivity to rifaximin; and clinically relevant abnormal laboratory values. All participants were required to test negative for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* by PCR, *Candida albicans* by microscopy, and *Trichomonas vaginalis* by culture or by PCR if negative by wet mount.

The study included a screening visit (V1), a randomization visit (V2), and 2 follow-up visits (V3, V4). Patients were evaluated for study eligibility at V1, and up to 7 days later were randomized at V2 by an interactive voice response system in a 1:1:1:1 ratio to receive a daily rifaximin vaginal tablet of 100 mg for 5 days (100 mg/5 days); a daily rifaximin vaginal tablet of 25 mg for 5 days (25 mg/5 days); a daily rifaximin vaginal tablet of 100 mg for 2 days, followed by daily placebo for 3 days (100 mg/2 days); or a daily placebo vaginal tablet for 5 days (placebo). The medication was dispensed by the investigator in accordance with a computer-generated random allocation sequence (SAS release 9.2; SAS Institute, Cary, NC, USA) prepared by a statistician who was not blind to the treatment regimen. Treatment regimens were also stratified by patient history of bacterial vaginosis (first bacterial vaginosis episode versus recurrent bacterial vaginosis).

Both investigator and patient were unaware of the treatment dispensed because the placebo was indistinguishable from the active substance, having the same weight, appearance, and color. Patients were instructed to insert 1 tablet of the study drug intravaginally at bedtime and then again daily at the same time for 5 days. Furthermore, they received a diary card to record intake and time of study medication, local subjective tolerability, and use of concomitant medications. At V3, 7–10 days after the end of therapy, patients who did not show therapeutic cure were withdrawn from the study as a treatment failure and received standard treatment, whereas patients showing cure attended V4, the second follow-up visit, 28–35 days after the end of treatment. Efficacy and safety assessments were performed at each follow-up visit; tests for *N. gonorrhoeae, C. trachomatis, C. albicans* and *T. vaginalis* were performed only if clinically indicated.

The primary efficacy endpoint was therapeutic cure of bacterial vaginosis (the combined presence of ≤2 Amsel criteria and a Nugent score of ≤3) at V3. Secondary efficacy endpoints were clinical cure according to Amsel criteria (≤2 criteria) at V3, bacteriologic cure according to Nugent score (≤3) at V3, and maintenance of therapeutic cure at V4.

Bacterial vaginosis diagnostics at V1, V3, and V4 comprised assessment for Amsel criteria (presence of vaginal discharge, vaginal pH measurement, microscopic examination of fresh vaginal fluid for the presence of clue cells, and "whiff test" with 10% potassium hydroxide), and Gram stain for Nugent score performed in an external laboratory not linked to the investigator site. Safety and adverse effects were evaluated on the basis of local objective signs (vaginal erythema, edema, petechial hemorrhages, ulcerations), subjective symptoms (vaginal pain, burning, itching, assessed on a 0–3 severity score), vital signs, physical and pelvic examination findings, and routine laboratory parameters.

NQueryAdvisor version 6.0 (Statistical Solutions, Munich, Germany) was used to estimate sample size on the basis of planned confirmative comparisons of the rifaximin treatment groups versus the placebo group with respect to therapeutic cure rates. The power estimation was based on a 2-sided Fisher exact test. Assuming a cure rate of 10% in the placebo group [19], a sample size of 22 patients per group would provide at least 80% power for each single comparison, resulting in a required overall sample size of 88 patients. Assuming a 20% rate of screening failures and a 20% drop-out rate, we planned to screen 140 patients to attain 112 randomized patients (28 patients per group).

The primary analysis of efficacy was performed on the full analysis set (FAS), which consisted of all patients who were randomized, took at least the first 3 consecutive doses of study medication, and attended at least 1 visit after randomization with available efficacy data. Analyses of primary and secondary endpoints for supportive and sensitivity purposes were also performed on the per protocol set, consisting of all patients who had completed the 5-day treatment according to the treatment schedule without protocol violations, to assess their influence on the study results.

Descriptive 95% Clopper–Pearson 2-sided confidence intervals of cure rates were calculated for each treatment group to enable further explorative comparisons among the different rifaximin dosage groups. Analyses of the secondary efficacy endpoints were performed in a manner similar to analysis of the primary endpoint and were purely descriptive. Safety analysis was based on the safety evaluation set, comprising all patients who received at least 1 dose of the study medication. Safety variables, that is adverse events, local objective and subjective tolerability, laboratory evaluations, vital signs, physical examination findings, and gynecologic signs and symptoms were analyzed via descriptive statistics.

Statistical analyses were performed using SAS version 9.2 (SAS Institute). Comparisons of the cure rates among individual active treatment groups, as well as between the pooled group of women receiving any dose of rifaximin and those receiving placebo, were performed using a 2-sided Fisher exact test. A P value of less than 0.05 was taken to be significant.

3. Results

Among 149 patients screened, 35 did not meet the inclusion criteria and were withdrawn before randomization. Of the 114 patients randomized, 106 proceeded to use the study medication (safety evaluation set), and 103 were evaluable for efficacy (FAS). The flow of patients through the study is shown in Fig. 1.

The demographic characteristics of the participants by treatment group are reported in Table 1. No relevant differences among the groups were detected at baseline. Approximately half of the patients in all groups reported bacterial vaginosis as a first episode, and there was an even prevalence of recurrent bacterial vaginosis among all 4 groups (Table 1).

Analysis of the primary efficacy endpoint in the FAS showed that the therapeutic cure rate at V3 was higher in the rifaximin 25 mg/5 days (48.0%, $P=0.04$), rifaximin 100 mg/2 days (36.0%), and rifaximin 100 mg/5 days (25.9%) groups than in the placebo group (19.0%) (Fig. 2). FAS results were confirmed by analysis based on the per protocol set. Subgroup analysis of the primary endpoint stratified by history of bacterial vaginosis showed a higher cure rate among patients with "recurrent bacterial vaginosis" than among patients with a "first episode of bacterial vaginosis" for all rifaximin groups. Among women with a first episode, those treated with the rifaximin 25 mg/5 days regimen responded better (therapeutic cure rate, 41.7%) than women treated with other rifaximin regimens or placebo (therapeutic cure rate, 14%–25%; $P=0.4$) (Table 2).