Original Article

Gynecologic and Obstetric Investigation

Gynecol Obstet Invest 2012;73:8–15
DOI: 10.1159/000332398

Received: March 30, 2011
Accepted: August 23, 2011
Published online: December 24, 2011

A Comparison of Dequalinium Chloride Vaginal Tablets (Fluomizin®) and Clindamycin Vaginal Cream in the Treatment of Bacterial Vaginosis: A Single-Blind, Randomized Clinical Trial of Efficacy and Safety

Ernst Rainer Weissenbacher[a] Gilbert Donders[b, c] Vit Unzeitig[f]
Begoña Martinez de Tejada[d] Stefan Gerber[e] Michael Halaška[g]
Jiří Špaček[h] Fluomizin Study Group

[a]Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, LMU München Grosshadern, Munich, Germany; [b]Department of Gynecology and Obstetrics, Algemeen Ziekenhuis Heilig Hart, Tienen, and [c]University Hospital Gasthuisberg, Leuven, Belgium; [d]Department of Obstetrics and Gynecology, University Hospitals of Geneva and Faculty of Medicine, Geneva and [e]Department of Obstetrics and Gynecology, CHUV, Lausanne, Switzerland; [f]Centrum ambulantní gynekologie a porodnictví and University Hospital, Brno, [g]Fakultní nemocnice Na Bulovce, Gynekologicko-porodnická klinika, Prague, and [h]Department of Obstetrics and Gynecology, University Hospital Hradec Králové, Hradec Králové, Czech Republic

Key Words

Bacterial vaginosis · Dequalinium chloride · Clindamycin · Vaginal infections · Local therapy · Pregnancy · Fluomizin®

Abstract

Aims: To investigate if vaginal application of dequalinium chloride (DQC, Fluomizin®) is as effective as vaginal clindamycin (CLM) in the treatment of bacterial vaginosis (BV). ***Methods:*** This was a multinational, multicenter, single-blind, randomized trial in 15 centers, including 321 women. They were randomized to either vaginal DQC tablets or vaginal CLM cream. Follow-up visits were 1 week and 1 month after treatment. Clinical cure based on Amsel's criteria was the primary outcome. Secondary outcomes were rate of treatment failures and recurrences, incidence of post-treatment vulvovaginal candidosis (VVC), lactobacillary grade (LBG), total symptom score (TSC), and safety. ***Results:*** Cure rates with DQC (C1: 81.5%, C2: 79.5%) were as high as with CLM (C1: 78.4%, C2: 77.6%). Thus, the treatment with DQC had equal efficacy as CLM cream. A trend to less common post-treatment VVC in the DQC-treated women was observed (DQC: 2.5%, CLM: 7.7%; p = 0.06). Both treatments were well tolerated with no serious adverse events occurring. ***Conclusion:*** Vaginal DQC has been shown to be equally effective as CLM cream, to be well tolerated with no systemic safety concerns, and is therefore a valid alternative therapy for women with BV [ClinicalTrials.gov, Med380104, NCT01125410].

Introduction

Bacterial vaginosis (BV) is the most common cause responsible for 20–40% of recurrent vaginal infections in women of childbearing age [1]. BV is a synergistic poly-

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0378–7346/12/0731–0008$38.00/0

Accessible online at:
www.karger.com/goi

E.R. Weissenbacher
LMU München Grosshadern
Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe
Marchioninistrasse 15, DE–81377 München (Germany)
Tel. +49 89 7095 4730, E-Mail ernst-rainer.weissenbacher@med.uni-muenchen.de

microbial syndrome characterized by depletion of *Lactobacillus* spp., especially those producing hydrogen peroxide, and an intense increase in the quantity of commensally anaerobic bacteria, such as *Gardnerella vaginalis* and other anaerobic Gram-negative rods [2, 3]. BV is associated with serious sequelae including increased susceptibility for sexually transmitted infections, development of pelvic inflammatory disease, and complications in pregnancy [3, 4]. A high recurrence rate of BV impairs the quality of life of affected women. The precise etiology of this syndrome is not well understood, and whether a shift in the existing vaginal flora or infection by other microbes leads to the development of BV is not clear [3, 4].

Currently, there are two internationally recommended first-line therapies, oral metronidazole or vaginal clindamycin (CLM) [5, 6], with similar 1-month cure rates of 60–90% [7, 8]. However, 15–30% of women have symptomatic recurrence 30–90 days following therapy, and 50–70% within 6–12 months [7, 8]. In addition, 12–24% of women develop vulvovaginal candidosis (VVC) following treatment [9, 10]. Increasing resistance against current therapies has been described by several investigators [11–14]. Goldstein et al. [12, 13] reported an increase of *G. vaginalis* resistance to metronidazole from 20 to 29% between 1993 and 2003. Another important and frequent microorganism in BV flora, *Atopobium vaginae*, is less responsive to metronidazole than to CLM [15].

Dequalinium chloride (DQC), a quaternary ammonium compound, has a wide range of antimicrobial activity against Gram-positive and -negative bacteria, fungi and protozoa [16, 17]. Its primary mode of action is the disruption of cell permeability and the subsequent loss of enzymatic activity [18]. The antimicrobial activity of DQC has been assessed in vitro, and the minimum inhibition concentrations against relevant vaginal pathogens have been established [16, 17]. The clinical efficacy and safety of DQC in the form of a vaginal tablet (Fluomizin®) or vaginal ovula in the treatment of BV and VVC have been previously demonstrated [19, 20].

The objective of this study was to compare the clinical efficacy and safety of vaginal tablets containing 10 mg DQC (Fluomizin) and CLM vaginal cream (2%) in women with BV.

Subjects and Methods

This was a single-blinded, randomized, active-controlled study with two parallel groups (DQC vs. CLM) of women with BV. Theoretically, women were possibly aware of which study drug they were using despite the blinded boxes, as one drug's formulation was a cream, while the other was a tablet. To overcome possible bias in the efficacy assessment by the investigator, two physicians were involved during the visits: the 'treating' physician dispensed the study medication according to randomization code and assessed compliance and side effects, and the 'evaluating' physician assessed the efficacy while blinded to the type of study medication given. This clinical trial was registered at EudraCT (2006-004398-89) and at ClinicalTrial.gov (Med380104, NCT01125410). The study was conducted in 15 centers in five countries in accordance with the Declaration of Helsinki and the GCP guidelines, and approved by all local Ethics Committees. All women gave written informed consent and were enrolled into the study from January 2007 to July 2008. This report complies with the CONSORT guidelines.

Premenopausal women aged 18–55 years were eligible for the study; 1 women aged 16 was included with the consent of her parents. To be included in the study, women had to be diagnosed with BV, for which all 4 Amsel criteria [21] had to be present: (1) characteristic grey, homogeneous, malodorous discharge, (2) pH >4.5, (3) a positive KOH test for amines, and (4) clue cells (positive if $\geq$20% of the epithelial cells of the wet mount were clue cells). Women were required to use effective contraception, but not involving materials sensitive to mineral oil. Exclusion criteria were pregnancy, lactation, hypersensitivity to the medications, uterine or vaginal bleeding, acute genital tract infections, ulcerations, VVC, use of anti-infectious or any vaginal medication, vaginal douches, genital malignancies, suspicion of or clinically manifested sexually transmitted infections, enteritis, ulcerative colitis or medical history of antibiotics-induced colitis. The study included one screening and two follow-up visits. Women were randomized to receive 10 mg DQC vaginal tablets (Fluomizin) for 6 days or CLM vaginal cream (2%) for 7 days. Follow-up visits took place 7 days (C1) and 25 days (C2) after the end of treatment. At C1 and C2, safety and tolerability of the medication were assessed by the 'treating' physician, whereas the 'evaluating' physician, blinded to the study medication, performed vaginal examination and assessed the efficacy variables. The primary efficacy outcome was clinical cure at C1 defined as absence of clue cells and a negative result for at least 2 other Amsel criteria. Secondary efficacy outcomes were clinical cure at C2, clinical improvement at C1 and C2 (2 or more Amsel criteria being negative), all single Amsel criteria, rate of treatment failures at C2 (recurrences and non-responders), incidence of clinical VVC, cultural presence of *Candida*, and lactobacillary grade (LBG). LBG evaluation was done by each investigator and LBGs were classified according to Donders et al. [22] as normal, grade-I flora (LBG I), intermediate, grade-II flora (LBG II), and abnormal, grade-III flora (LBG III). Furthermore, total symptom score (TSC; calculated as the sum of the individual scores (0–3) for discharge, pruritus and burning) and global assessment of efficacy were evaluated. Treatment compliance was assessed using a patient's diary. Safety (SAF) outcomes were incidence of adverse events (AEs), serious AEs, and adverse drug reactions (ADRs) as well as global assessment of tolerability.

The study used a two-stage adaptive design according to Bauer and Köhne [23] with a pre-specified interim analysis to adapt the sample size. The initial sample size was based on the primary variable and a power of 90%. The primary analysis was the per-protocol-set (PPS) analysis performed for clinical cure rate at C1.

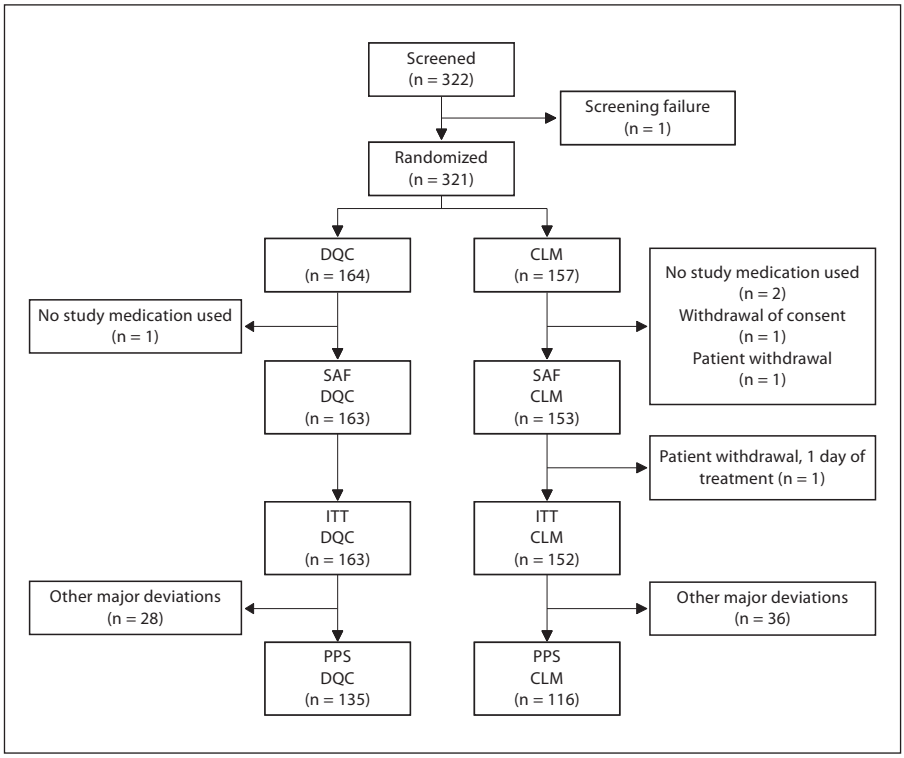

Fig. 1. Patient disposition.

Table 1. Patient demographics (ITT, n = 315)

	DQC (n = 163)	CLM (n = 152)
Median age, years (range)	32 (16–54)	31 (18–60)
Caucasian, n (%)	163 (100)	150 (98.7)
Mean weight, kg (SD)	62.8 (10.2)	62.4 (11.3)
Mean BMI (SD)	22.3 (3.3)	22.4 (3.7)
Women with prior vaginal infection		
≥1 prior BV, n (%)	113 (69.3)	109 (71.7)
0 prior vaginal infection, n (%)	39 (23.9)	36 (23.7)
Hormonal contraception, n (%)	105 (64.4)	105 (69.1)

SD = Standard deviation; BMI = body mass index.

Clinical cure rates were analyzed both for the PPS and the intention-to-treat (ITT) population. All other efficacy variables were analyzed based on ITT population. Safety analysis included all women who received at least one dose of the study medication. Clinical cure and clinical improvement rates were tested for non-inferiority (15% inferiority margin; one-sided test, 2.5% significance level) applying the maximum likelihood test according to Farrington and Manning [24]. Due to the two-stage adaptive design, a critical value c_α of 0.0038 for the product of the maximum likelihood p values from the first (interim analysis) and second (data after interim analysis) step was used, and the two-sided 95% confidence intervals (with a pre-specified non-inferiority margin of –15%) for the complete study population (overall cure rate) was determined. Non-inferiority was demonstrated if $p_1 \times p_2 \leq c_\alpha = 0.0038$ and the two-sided 95% confidence interval ($CI_{95\%diff}$) was [–15%; 15%]. TSC and global efficacy were compared by the Mann-Whitney test [25]. For other secondary efficacy variables, the χ^2 test was performed. Other demographic and safety parameters were analyzed descriptively.

Results

Demographics and baseline characteristics of the two study groups were comparable (table 1). A total of 321 women were randomized to receive either DQC (n = 164) or CLM (n = 157) (fig. 1). The mean time between end of treatment and control visits were 7 days (C1) and 25 days (C2), respectively. The SAF population included 316 women, 163 in the DQC group and 153 in the CLM group. One woman randomized to the CLM group was excluded from the ITT population since she withdrew her consent after 1 day of treatment. After a blind data review, 64 women from the ITT population were identified having major protocol deviations, leading to an exclusion from the PPS population (n = 28 in the DQC

Table 2. Clinical cure rate

	Total, n	Missing, n	Cured, n	Cure rate, %	$CI_{95\%diff}$	Difference DQC – CLM, $p_1 \times p_2$
Follow-up visit C1						
PPS						
DQC	135	–	110	81.5	–0.07, 0.13	p_1 (0.02202) × p_2 (0.00177) = 0.00004
CLM	116	–	91	78.4		
ITT						
DQC	163	5	126	79.7	–0.08, 0.10	p_1 (0.02127d) × p_2 (0.00172) = 0.00004
CLM	152	11	111	78.7		
Follow-up visit C2						
PPS						
DQC	135	3	105	79.5	–0.08, 0.12	p_1 (0.00718c) × p_2 (0.02317) = 0.00017
CLM	116	–	90	77.6		
ITT						
DQC	163	8	116	74.8	–0.10, 0.10	p_1 (0.00398d) × p_2 (0.08305) = 0.00033
CLM	152	9	107	74.8		

$p_1 \times p_2$ = Product p values from the first (interim analysis) and second (data after interim analysis) step: non-inferiority if <0.0038.

group, n = 36 in the CLM group; one or more violations per woman were possible). The most common protocol deviations were time window violations (n = 12 in both groups), prior termination (DQC: n = 5; CLM: n = 9), the investigator acted as 'treating' and 'evaluating' physician for the same woman (DQC: n = 9; CLM: n = 7) and violations of inclusion or exclusion criteria (DQC: n = 4; CLM: n = 6). There were no apparent differences in major protocol violations between the groups. Therefore, the PPS population included 135 women in the DQC group and 116 women in the CLM group. From the ITT population, 13 women in the DQC group and 15 in the CLM group did not complete the study. Based on the patient's diary, 95.1% of women in the DQC group and 88.9% in the CLM group complied with the treatment schedule.

Clinical cure rates at C1 (primary variable) in the PPS population were 81.5% in women treated with DQC and 78.4% in CLM-treated women (table 2). The $CI_{95\%diff}$ for the difference in clinical cure of DQC and CLM was [–6.9%; 13.0%], and thus within the pre-specified non-inferiority margin of ±15%. Therefore, non-inferiority of DQC versus CLM was demonstrated.

At C2, the clinical cure rates observed in the PPS population were 79.5% with DQC and 77.6% with CLM, $CI_{95\%diff}$ = [–8.3%; 12.2%], demonstrating efficacy of DQC was not inferior to that of CLM. For the ITT population, overall cure rates at C1 and C2 were comparable supporting the PPS results (table 2). Clinical improvement rates in DQC- and CLM-treated women were 88.6 and 92.3% at C1 ($CI_{95\%diff}$ = [–10.8%; 3.5%]), and 79.3 and 85.3% at C2 ($CI_{95\%diff}$ = [–14.8%; 2.9%]). Other secondary efficacy variables are shown in table 3. Most Amsel criteria were comparable without relevant differences between the groups. Only at C1, vaginal pH was significantly more often below 4.5 in the DQC group than in the CLM group (p = 0.02). The rate of non-responders at C2 in the DQC group was slightly lower than in the CLM-treated women, whereas the rate of recurrences was slightly higher with DQC than with CLM, but none of these differences were significant. The total failure rate (non-responders and recurrences combined) was similar for DQC and for CLM.

During the complete study, 4 women (2.5%) in the DQC group and 11 (7.7%) in the CLM group were diagnosed with symptomatic, culture positive VVC (p = 0.06). The numbers of women in each group showing symptoms of clinical VVC or positive cultures for *Candida* spp. were not significantly different (table 3). However, both numbers increased from C1 to C2 in the CLM group, but not in the DQC group.

At entry, about 75% of women in both groups presented with an abnormal LBG III flora. This percentage of women was strongly reduced after the treatment in both groups (table 3). The cure rates at C2 for women with LBG III at entry were similar to the entire population, i.e. 74.2% in the DQC group and 70.9% in the CLM group. No significant difference between the groups was ob-

Table 3. Secondary efficacy variables (ITT, n = 315)

	DQC (n = 163)	CLM (n = 152)	p value*
Amsel criteria, n (%)			
Discharge			
C1	29 (18.4)	19 (13.3)	0.23
C2	30 (20.0)	23 (16.8)	0.48
Vaginal pH >4.5			
C1	65 (41.1)	78 (54.5)	0.02
C2	57 (38.0)	60 (43.8)	0.32
Clue cells >20%			
C1	21 (13.3)	16 (11.2)	0.58
C2	25 (16.7)	19 (13.9)	0.51
Positive KOH test			
C1	17 (10.8)	15 (10.5)	0.94
C2	25 (16.7)	17 (12.4)	0.31
Non-responders and recurrences, n (%)			
Non-responders	17 (10.4)	23 (15.2)	0.21
BV recurrence	22 (13.5)	14 (9.2)	0.23
Total failures	39 (23.9)	37 (24.3)	0.93
Incidence of clinical VVC, n (%)			
C1	5 (3.2)	4 (2.8)	1.00
C2	4 (2.7)	8 (5.8)	0.24
Presence of *Candida* spp., n (%)			
Entry	12 (7.4)	8 (5.3)	0.45
C1	21 (13.3)	16 (11.2)	0.58
C2	14 (9.3)	20 (14.6)	0.17
LBG, n (%)			
Entry			
LBG I	1 (0.6)	1 (0.7)	
LBG II	37 (22.7)	38 (25.0)	
LBG III	125 (76.7)	113 (74.3)	0.89
C1			
LBG I	90 (57.0)	79 (55.2)	
LBG II	49 (31.0)	38 (26.6)	
LBG III	19 (12.0)	24 (16.8)	0.42
C2			
LBG I	101 (67.3)	80 (58.4)	
LBG II	33 (22.0)	40 (29.2)	
LBG III	16 (10.7)	16 (11.7)	0.30
TSC, mean ± SD (n)			
Entry	3.7 ± 2.0 (163)	4.1 ± 2.0 (152)	0.14
C1	1.0 ± 1.7 (158)	1.0 ± 1.7 (142)	0.58
C2	0.7 ± 1.4 (150)	1.0 ± 1.7 (137)	0.08

* χ^2 test or Fisher's exact test.

Table 4. Global efficacy (ITT, n = 315)

	DQC (n = 163)	CLM (n = 152)	p value*
Investigators, very good or good			
C1, n (%)	117 (74.1)	106 (74.1)	0.84
C2, n (%)	104 (69.3)	98 (71.5)	0.27
Patients, very good or good			
C1, n (%)	131 (82.9)	110 (76.9)	0.41
C2, n (%)	111 (74.0)	103 (75.2)	0.59

* χ^2 test.

served regarding LBG. Mean TSC decreased in both groups from approximately 4 at entry visit to ≤1 at C2 in both treatment groups (p = 0.08; table 3). There were no differences in the global efficacy assessments by investigator and patient (table 4).

During this study, no serious AEs were observed. Fewer AEs were experienced by women treated with DQC (134) than by women treated with CLM (163) and a lower proportion of women in the DQC group reported at least one AE, but none of these differences in AEs and ADRs were statistically significant (table 5). The most frequently reported ADRs in both the DQC- and CLM-treated women were vaginal discharge (9.2 and 4.6% of women, respectively) followed by vulvovaginal pruritus (4.9 and 8.5% of women, respectively). At visits C1 and C2, the majority of investigators and women (>90%) judged the overall tolerability of treatment as very good or good, with no apparent difference between the groups.

Discussion

In this study, we have shown that treatment of BV with a 6-day course of vaginal tablets containing 10 mg DQC (Fluomizin) has equal efficacy as a 7-day course of CLM vaginal cream (2%). Clinical cure rates at 1 week after the end of therapy (C1) were similar in both groups. Also the cure rates at about 4 weeks after the end of therapy (C2) were comparable in both treatment groups. We used a very stringent definition for BV diagnosis in order to be included in the study: all 4 Amsel criteria had to be positive. Therefore, women with partial BV [26] or in whom diagnosis was not 100% sure were not included. Similarly, the criteria for establishing clinical cure required absence of clue cells and a negative result for at least 2 other Amsel criteria, adding to the strength of this study.

The efficacy of CLM has been assessed in previous clinical studies mainly by using only 3 of the 4 Amsel criteria (pH >4.5, clue cells, and KOH test). In ten clinical studies with CLM a total of 600 women have been treated; the clinical cure rate (absence of the 3 criteria) was 53.4% (37–72%) and the clinical improvement rate (not more

Table 5. Frequently reported adverse events (n = 316)

	DQC (n = 163), n (%)	CLM (n = 153), n (%)	p value*
Adverse events (AEs)			
Number of AEs	134	163	
Number of women with AEs	66 (40.5)	73 (47.7)	0.20
Related AEs			
Number of related AEs	54	48	
Number of women with related AEs	29 (17.8)	31 (20.3)	0.58

* Fisher's exact test.

Table 6. Cure rate comparison (ITT, n = 315)

	Follow-up visit C1			Follow-up visit C2		
	DQC (n = 163)	CLM (n = 152)	p value*	DQC (n = 163)	CLM (n = 152)	p value*
Based on all 4 Amsel criteria						
Cured[a] – no clue cells and ≥2 others negative	79.7%	78.7%	0.83	74.8%	74.8%	1.00
Cured – all 4 negative	52.9%	41.8%	0.06	56.7%	50.4%	0.29
Improved – ≥3 of 4 negative	80.4%	79.4%	0.84	79.3%	80.0%	0.89
Based on 3 Amsel criteria[b]						
Cured – all 3 negative	58.2%	44.0%	0.01	60.0%	53.3%	0.26
Improved – ≥2 of 3 negative	84.2%	83.7%	0.91	80.7%	83.8%	0.49

* χ^2 test. [a] Primary efficacy variable of this study. [b] pH >4.5, clue cells, KOH test.

than 1 positive) was 73.4% (65–94%) [8]. Using this definition for the cure rate at C2, 60.0% of women treated with DQC and 53.3% in the CLM group were cured in the current study. To facilitate the comparison of our results with previous study results for CLM and metronidazole, differently defined cure and improvement rates are summarized in table 6. Overall, based on the various definitions, the cure rates observed in our study were comparable with the ones of previous reports using CLM and/or metronidazole [3, 8, 27].

Recurrence of BV is known to occur commonly, regardless of which antibiotic treatment is used [3, 27]. Analysis of non-responders and BV recurrence at visit C2 showed no significant difference between DQC- and CLM-treated women. We also assessed secondary efficacy parameters including clinical improvement, TSC, individual Amsel criteria and LBG. DQC showed consistently equal efficacy as vaginal CLM for the treatment of BV, except for the vaginal pH. There were significantly more women with a normal vaginal pH at C1 in the DQC group than in the CLM group. This finding together with a trend for a higher percentage of women with LBG I at C2 might indicate a better recovery of the normal vaginal flora under DQC therapy. It is known that CLM may have a detrimental effect on lactobacillary species, making it more timely (up to 1 month) and difficult to obtain a full recovery of the normal flora [28]. This has led some authors to advocate the use of probiotics after CLM treatment to hasten the full recovery of the vaginal flora [29, 30].

The number of women with subsequent VVC was low in both groups as compared to previous reports [9, 10]. There was no statistical difference between the groups regarding symptoms of clinical VVC or positive cultures for *Candida* spp. However, the difference between the groups regarding women diagnosed with clinical VVC and concomitant positive culture was at the limit of the statistical significance.

The safety profiles of the two study treatments were similar in terms of the types of AEs, and no significant difference was observed regarding the incidence of AEs and ADRs.

Metronidazole and CLM taken orally or applied vaginally are the current mainstays of therapy for BV. However, both are ineffective in approximately 10–40% of patients, [3, 27] are associated with a high recurrence rate [7, 8], an increased likelihood of post-treatment VVC [9, 10], and not devoid of a risk of developing resistance, especially if given repetitively [11–14]. DQC is an anti-infective agent with a different mode of action, targeting the microbial cytoplasm membrane and leading to release of cellular components [18]. Due to this general mode of action, DQC comprises a broader spectrum of antimicrobial activity than most antibiotics and exerts a rapid microbiocidal action against a variety of pathogens [16, 17]. We have shown in our study that DQC is as effective as one of the recommended regimens with maybe a faster recovery of the normal vaginal flora.

Fluomizin vaginal tablets containing 10 mg DQC may have the following advantages: it has a broad antimicrobial spectrum, it is less vulnerable to resistance, a high concentration of the substance at the infection site can be achieved, while systemic exposure is negligible. All this can offer a strong benefit for the treatment of women with BV, particularly also as a safe therapeutic alternative during pregnancy.

We conclude that treatment with vaginal tablets containing 10 mg DQC (Fluomizin) results in similar cure rates as one of the current standard therapies for BV and is well tolerated with no systemic safety concerns. Therefore, DQC is a valid treatment for BV as it is CLM vaginal cream (2%).

Acknowledgements

In addition to the main authors, the Fluomizin Study Group included the following gynecologists, whom the authors would like to thank: Dr. Florian Bergauer, Germany, Dr. Jan Bosteels, Belgium, Dr. Josef Chovanec, Czech Republic, Dr. Jan Danko, Slovak Republic, Dr. Piet Hinoul, Belgium, Dr. Jaromír Mašata, Czech Republic, Dr. Jan Řičánek, Czech Republic, and Dr. Luc Verguts, Belgium. The authors would like to thank Dr. Philipp Grob, Switzerland, Dr. Valdas Prasauskas, Switzerland, and Dr. Olaf Böhm, Germany, for their comments concerning the manuscript.

Disclosure Statement

This study and online FreeAccess publication was sponsored by Medinova AG, Zurich, Switzerland. None of the authors or study group members reports any conflict of interest concerning this study.

References

1 Sobel JD: Vaginitis. N Engl J Med 1997;337:1896–1903.
2 Forsum U, Holst E, Larsson PG, Vasquez A, Jakobsson T, Mattsby-Baltzer I: Bacterial vaginosis – a microbiological and immunological enigma. APMIS 2005;113:81–90.
3 Sobel JD: Bacterial vaginosis. Annu Rev Med 2000;51:349–356.
4 O'Brien RF: Bacterial vaginosis: many questions – any answers? Curr Opin Pediatr 2005;17:473–479.
5 Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines 2002. MMWR Recomm Rep 2002;51:1–78.
6 British Association for Sexual Health and HIV (BASHH), Clinical Effectiveness Group (Association for Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases): National guideline for the management of bacterial vaginosis (www.bashh.org/guidelines).
7 Bradshaw CS, Morton AN, Hocking J, Garland SM, Morris MB, Moss LM, Horvath LB, Kuzevska I, Fairley CK: High recurrence rates of bacterial vaginosis over the course of 12 months after oral metronidazole therapy and factors associated with recurrence. J Infect Dis 2006;193:1478–1486.
8 Larsson PG, Forsum U: Bacterial vaginosis – a disturbed bacterial flora and treatment enigma. APMIS 2005;113:305–316.
9 Ferris DG, Litaker MS, Woodward L, Mathis D, Hendrich J: Treatment of bacterial vaginosis: a comparison of oral metronidazole, metronidazole vaginal gel, and clindamycin vaginal cream. J Fam Pract 1995;41:443–449.
10 Schmitt C, Sobel JD, Meriwether C: Bacterial vaginosis: treatment with clindamycin cream versus oral metronidazole. Obstet Gynecol 1992;79:1020–1023.
11 Austin MN, Beigi RH, Meyn LA, Hillier SL: Microbiologic response to treatment of bacterial vaginosis with topical clindamycin or metronidazole. J Clin Microbiol 2005;43:4492–4497.
12 Goldstein EJ, Citron DM, Cherubin CE, Hillier SL: Comparative susceptibility of the *Bacteroides fragilis* group species and other anaerobic bacteria to meropenem, imipenem, piperacillin, cefoxitin, ampicillin/sulbactam, clindamycin and metronidazole. J Antimicrob Chemother 1993;31:363–372.
13 Goldstein EJ, Citron DM, Merriam CV, Warren YA, Tyrrell KL, Fernandez HT: In vitro activities of Garenoxacin (BMS 284756) against 108 clinical isolates of *Gardnerella vaginalis*. Antimicrob Agents Chemother 2002;46:3995–3996.
14 Nagaraja P: Antibiotic resistance of *Gardnerella vaginalis* in recurrent bacterial vaginosis. Indian J Med Microbiol 2008;26:155–157.
15 DeBacker E, Verhelst R, Verstraelen H, Claeys G, Verschraegen G, Temmerman M, Vaneechoutte M: Antibiotic susceptibility of *Atopobium vaginae*. BMC Infect Dis 2006;6:51.

16 D'Auria FD, Simonetti G, Strippoli V: Antimicrobial characteristics of a tincture of dequalinium chloride (in Italian). Ann Ig 1989; 1:1227–1241.
17 Della Casa V, Noll H, Gonser S, Grob P, Graf F, Pohlig G: Antimicrobial activity of dequalinium chloride against leading germs of vaginal infections. Arzneimittelforschung 2002;52:699–705.
18 Hugo WB, Frier M: Mode of action of the antibacterial compound dequalinium acetate. Appl Microbiol 1969;17:118–127.
19 Petersen EE, Weissenbacher ER, Hengst P, Spitzbart H, Weise W, Wolff F, Dreher E, Ernst U, Della Casa V, Pohlig G, Graf F, Kaiser RR: Local treatment of vaginal infections of varying etiology with dequalinium chloride or povidone iodine. A randomised, double-blind, active-controlled, multicentric clinical study. Arzneimittelforschung 2002; 52:706–715.
20 Strecker M, Kokemohr H, Teucher T, Schmitz H: Antiseptika gegen Vulvovaginitiden. TW Gynäkol 1993;6:409–412.
21 Amsel R, Totten PA, Spiegel CA, Chen KCS, Eschenbach DA, Holmes KK: Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiological associations. Am J Med 1983;74:14–22.
22 Donders GG, Vereecken A, Dekeersmaecker A, van Bulck B, Spitz B: Wet mount microscopy reflects functional vaginal lactobacillary flora better than Gram stain. J Clin Pathol 2000;53:308–313.
23 Bauer P, Köhne K: Evaluation of experiments with adaptive interim analyses. Biometrics 1994;50:1029–1041.
24 Farrington CP, Manning G: Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stad Med 1990;9:1447–1454.
25 Mann H, Whitney D: On a test of whether one of two random variables is stochastically larger than the other. Ann Math Statist 1947; 50–60.
26 Donders GG: Definition and classification of abnormal vaginal flora. Best Pract Res Clin Obstet Gynaecol 2007;21:355–373.
27 Koumans EH, Markowitz LE, Hogan V: Indications for therapy and treatment recommendations for bacterial vaginosis in nonpregnant and pregnant women: a synthesis of data. Clin Infect Dis 2002;35:S152–S172.
28 Agnew KJ, Hillier SL: The effect of treatment regimens for vaginitis and cervicitis on vaginal colonization by lactobacilli. Sex Transm Dis 1995;22:269–273.
29 Larsson PG, Stray-Pedersen B, Ryttig KR, Larsen S: Human lactobacilli as supplementation of clindamycin to patients with bacterial vaginosis reduce the recurrence rate; a 6-month, double-blind, randomized, placebo-controlled study. BMC Womens Health 2008;8:3.
30 Ozkinay E, Terek MC, Yayci M, Kaiser R, Grob P, Tuncay G: The effectiveness of live lactobacilli in combination with low dose oestriol (Gynoflor) to restore the vaginal flora after treatment of vaginal infections. BJOG 2005;112:234–240.