ELSEVIER

Contraception

Contraception 67 (2003) 305–312
Original research article

A 12-month evaluation of the CMA-containing oral contraceptive Belara®: efficacy, tolerability and anti-androgenic properties

Georg Schramm*, Doris Steffens

Medical Department, Grünenthal GmbH, Zieglerstraße 6, 52078 Aachen, Germany

Received 24 September 2002; received in revised form 4 December 2002; accepted 10 December 2002

Abstract

Objectives: We conducted a postmarketing surveillance study to assess the long-term efficacy and tolerability of the oral contraceptive Belara® (chlormadinone acetate 2.0 mg/ethinylestradiol 0.03 mg) in a normal outpatient setting. Another interest focused on changes in androgen-related skin and hair disorders.
Methods: A total of 2620 women were enrolled in a 12-cycle clinical evaluation at 435 gynecological practices throughout Germany.
Results: An unadjusted Pearl index of 0.44 was calculated. At least 9 out of 10 pregnancies were attributable to user failure, thus resulting in an adjusted Pearl index of 0.04. More than two thirds (67.3%) of the women did not experience any bleeding disorder. Patients with intermenstrual bleeding or amenorrhea at study entry reported complete relief in 61.7% and 89.3%, respectively. Women who previously suffered from spots or bad skin showed significant improvement during the observation period (85.6%). Likewise, the percentage of patients with greasy or very greasy hair decreased markedly. The vast majority of women scored the tolerability of Belara as "very good" or "good."
Conclusions: The results of this postmarketing study confirm that Belara is well tolerated and provides a high contraceptive efficacy, reliable cycle stability and beneficial effects on skin and hair.

Keywords: Chlormadinone acetate; Ethinylestradiol; Oral contraceptive; Contraceptive efficacy; Cycle control; Androgenization; Adverse events

1. Introduction

Since 1959, oral hormonal contraceptives (OCs) have been available as a highly effective and well-accepted method for fertility control. Until now, more than 150 million women have taken OCs and, today, 60–80 million women are using OCs daily for contraception [1]. However, OC users not only expect optimal contraceptive efficacy and a reliable safety profile, but also additional benefits to general well-being. High-level cycle control, with minimal breakthrough bleeding or spotting and regular withdrawal bleeding are appreciated in particular. These aspects have a major influence on women's decisions about method continuation and compliance.

Indeed, symptoms detracting well-being, such as intermenstrual bleeding, dysmenorrhea, breast pain and migraine/headache, are commonly seen in daily gynecological practice. In many cases, clinical signs of androgenization, namely, seborrhea, acne, hirsutism and alopecia, accompany them [2]. While these androgen-related skin and hair changes are cosmetic rather than serious, they often cause significant emotional and psychological problems.

Over the last decades, a broad range of distinct OCs has become available to adapt to different therapeutic profiles and to meet individual needs. The present trend in combined oral contraceptives development is to reduce the estrogen content in order to minimize serious side effects, without compromising contraceptive efficacy [3]. By that, the characteristics of the progestogen component became more apparent. In the meantime, progestogens with weak or no androgenic effects, or even with antiandrogenic properties, have been developed. The latter has proven to be a useful approach to minimize androgen-related skin and hair disorders arising from hormonal imbalance [4,5].

Belara® (EE/CMA) is a monophasic combined low-dose oral contraceptive containing 0.03 mg ethinylestradiol (EE) and 2 mg chlormadinone acetate (CMA). The C_{21}-progestin CMA shows marked antiandrogenic properties. It reduces clinical manifestations of androgen-related disorders by competing with endogenous androgens at their receptors in

* Corresponding author. Tel.: +49-241-569-1239; fax: +49-241-569-2875.
E-mail address: Georg.Schramm@grunenthal.de (G. Schramm).

0010-7824/03/$ – see front matter
doi:10.1016/S0010-7824(02)00536-X

the sebaceous gland cells and by inhibiting 5_{α}-reductase type I [6–9]. The latter converts testosterone to its more active compound, dihydrotestosterone, which, in turn, stimulates the activity of the sebaceous glands [10].

CMA and EE have complementary actions in reducing androgen activity [6]. Along with this, CMA is expected not to interfere with the estrogen-related effects, including both cardiovascular protection [11] and antiandrogenic properties [12]. Thus, the combination of EE and CMA is deemed to be a logical choice not only for contraception, but also for the treatment of androgen-related conditions.

In a multicenter, phase III trial over 24 cycles in 1655 women, Belara was well tolerated and demonstrated remarkable benefits for hair and skin, excellent results for cycle stability and a reliable contraceptive efficacy (adjusted Pearl index of 0.27) [12].

Belara has been marketed in Germany since 1999, and there is now a great deal of experience with this low-dose oral contraceptive. To comply with the regulatory guidelines for newly marketed drugs in Germany, postmarketing surveillance studies are required to confirm the results of premarketing clinical trials. As such, the aim of this 12-cycle postmarketing study was to collect further information about the efficacy and tolerability of Belara during long-term routine clinical use. In addition, the influence of Belara on androgen-related disorders was evaluated.

2. Methods

2.1. Study subjects and design

This open multicenter observational clinical evaluation was conducted according to the German Drug Law and the quality standards issued by the German Health Authority (1998). The study protocol has been approved by the local Ethics Committees.

Four-hundred and thirty-five office-based gynecologists throughout Germany were involved in the postmarketing study. They were requested to document the intake of Belara (CMA 2 mg/EE 0.03 mg) over a period of 12 menstrual cycles. The observation period was between April 1999 and August 2000. Each gynecologist received study files for documenting data for up to eight women starting on the chlormadinone-containing oral contraceptive. Using a non-interventional design, Belara had to be prescribed according to the discretionary clinical judgement of the gynecologist, with inclusion and exclusion criteria limited to the licensed indications and contraindications (as stated in the prescribing information). Thus, data were only to be documented if patients were planned for a prescription of Belara anyway.

The women were classified as "starters" if they had never used an oral contraceptive before, and as "switchers" if they had changed directly from another brand to Belara or if they reported that they had previously taken another OC. Each woman took one Belara tablet on days 1–21 of the cycle, followed by a 7-day pill-free interval during which withdrawal bleeding usually occurred before starting the next cycle of treatment.

2.2. Evaluation and efficacy criteria

At baseline, the following parameters were documented: women's age, height and body weight, anamnestical data (tobacco consumption, adiposity, risk factors for the intake of OCs, family history of thromboembolic events), previous OC use, menstrual cycle history (last two cycles before Belara intake) and symptoms (e.g., headache, breast pain, tiredness). All documented symptoms had to be assessed as "mild", "moderate" or "severe." Furthermore, skin and hair type were to be noted on a scale between "very dry" to "very greasy" and, additionally, evaluated as for skin spots and frequency of hair washing. For each woman, the "normal" body weight was assessed by subtracting a value of 100 from the body height, which was expressed in metric terms. A woman was classified overweight if her body weight amounts to 10% above the normal weight and as underweight if the body weight was 20% below the normal weight.

At the end of the observation period, the physicians recorded cycle control (intermenstrual bleeding, intensity of withdrawal bleeding, dysmenorrhea), adverse events and symptoms, regular intake and premature withdrawal of Belara, changes in skin (spots) and hair type (greasiness/dryness, frequency of hair washing), weight change, tolerability and the wish to continue with Belara treatment. The tolerability was scored both by the investigator and the patient as "very good," "good," "medium" or "poor." Each documented complaint, symptom or sign of a disease was called a symptom, irrespective of whether it already occurred before the first dose of Belara intake. Symptoms that increased in intensity during Belara treatment, as well as new symptoms, were classified to be an adverse event. In other words, adverse events represent a subgroup of symptoms. Contraceptive efficacy was evaluated by calculating the Pearl index, which is valid because this is a 12-month study (for longer periods, life-table statistics are required).

2.3. Statistical analysis

The evaluation included all patients who have been prescribed Belara. For women not returning for the final examination after 12 months, at least cycle anomalies, AEs or other symptoms, which occurred during the first cycles of Belara intake, had been documented. If a patient stopped taking Belara before the end of the observation period, the physician recorded the last intake cycle as well as the reason for withdrawal. The documented data were analyzed using descriptive statistics. Metrical results were described by at least minimum, maximum, mean average value, standard deviation, median, 25% and 75% percentile. The Pearl index (PI) was determined by using the following formula:

Table 1
Clinical characteristics of the study population at baseline

Clinical characteristics	Number of subjects (% of total)[a]
Withdrawal bleeding	
Mild	560 (21.4)
Normal	1651 (63.0)
Severe	382 (14.6)
Not stated	27 (1.0)
Intermenstrual bleeding	
No	1777 (67.8)
Yes	817 (31.2)
Not stated	26 (1.0)
Amenorrhea	
No	2183 (83.3)
Yes	400 (15.3)
Not stated	37 (1.4)
Dysmenorrhea	
No	1324 (50.3)
Mild	879 (33.6)
Severe	387 (14.8)
Not stated	30 (1.2)
Skin condition	
Greasy or very greasy	697 (26.6)
Slightly greasy	931 (35.5)
Normal	647 (24.7)
Dry	335 (12.8)
Not stated	10 (0.4)
Hair type	
Greasy or very greasy	1327 (50.6)
Normal	1083 (41.3)
Dry	198 (7.6)
Not stated	12 (0.5)

[a] N = 2620; mean age (years) ± SD: 24.5 ± 7.4; range: 13–49 years.

$$\mathrm{PI} = \frac{\text{number of pregnancies} \times 1300}{\text{number of treatment cycles}}$$

The calculation also included the assessment of the corresponding 95% confidence interval (CI). Due to the non-interventional study design, no statistical significance of any differences has been formally analyzed.

3. Results

A total of 2620 patients from 435 gynecological practices took part in the observation study and were treated with Belara for <12 month. The analysis thus encompassed 29,262 cycles of exposure. No patients were excluded from the evaluation.

3.1. Baseline characteristics

3.1.1. Age, risk factors and previous intake of OCs

The mean age of the entire study population at baseline was 24.5 + 7.4 years (Table 1), with about one quarter of the women aged younger than 19 years, and a further 45% aged 19–28 years. Corresponding to the weight classification described before, 8.0% of the women were found to be overweight and 33.5% were smokers. Of these, almost two thirds stated a daily consumption of 1–10 cigarettes. Varicosis was observed in 24 patients (0.9%) and a positive family history of thromboembolic diseases was documented in 65 women (2.5%). Venous thromboembolic events (VTEs) occurred in the families of 35 patients (1.3%).

At entry, 36.9% of all women took an oral contraceptive for the first time as part of this observation study (pill "starters"). In comparison, 63.1% changed directly from another pill or used to take OCs in the past (pill "switchers"). Of these, 13.9% switched from Valette®, 12.2% from Diane-35®, 9.1% from Neo-Eunomin®, 5.7% from Microgynon® and 5.4% from Leios®. Other OCs represented <5.0%.

3.1.2. Clinical characteristics

The clinical characteristics (i.e., menstrual cycle history, skin condition and hair status) are shown in Table 1. About 15% of all women suffered from severe withdrawal bleeding within the last two cycles before taking Belara. More than 30% reported intermenstrual bleeding, and amenorrhea occurred in 15% of the patients. Almost half of the women reported suffering from mild or severe dysmenorrhea.

Other OC-typical complaints were stated by 872 patients (33.3%). Among them, headache/migraine (29.2% of patients with symptoms), breast pain (28.4%), androgenization disorders (26.1%), depression (12%), weight gain (5.8%) and tiredness (5.3%) were documented most commonly. These symptoms were classified as mild in 21%, in 48.0% as moderate, and in 27% as severe. For the remaining 4%, no data were available.

At baseline, 71.2% of all women suffered from spots or bad skin. Greasy skin conditions were found in more than 60% of the patients and approximately half of the women stated their hair type as greasy or very greasy. Likewise, the majority of patients preferred hair washing daily (23.8%) or at least every 2 days (39.0%).

3.2. Contraceptive efficacy

The study comprised 29,262 cycles in 2620 women. Of these, a total of 10 women became pregnant during the 12-month observation period. Thus, the unadjusted Pearl index was calculated to be 0.4 [95% CI (0.2, 0.8)]. However, intake errors were considered to be responsible for 90% of the undesired pregnancies with at least eight out of nine patients who forgot to take Belara several times. After review, in only one case was a method failure stated as possible, resulting in an adjusted Pearl index of 0.04 [95% CI (0.002, 0.2)].

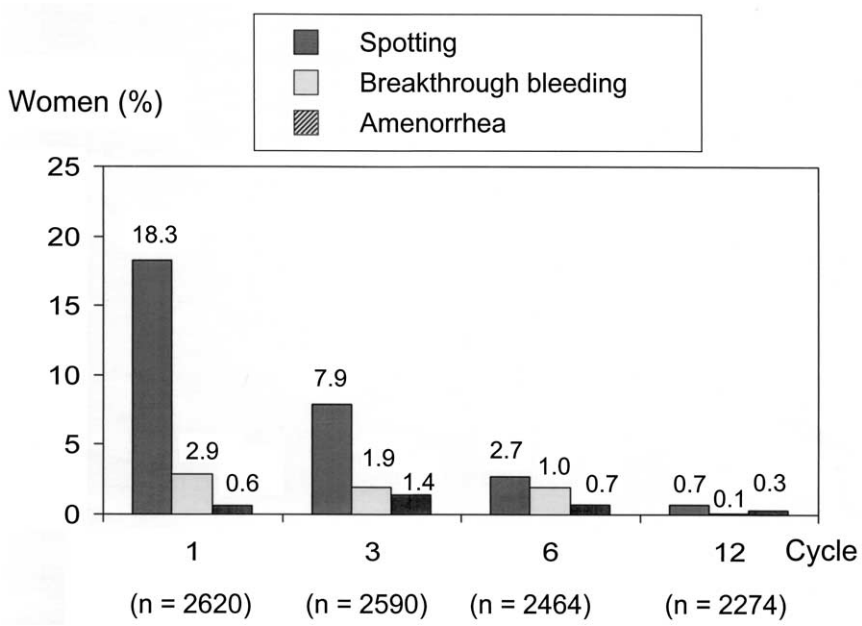

Fig. 1. Menstrual bleeding disorders per cycle during Belara® intake.

3.3. Cycle control

3.3.1. Menstrual bleeding disorders

During the intake of Belara, 67.3% of all women did not experience any bleeding disorder. Slight intermenstrual bleeding (spotting), breakthrough bleeding and amenorrhea were documented in 26.6%, 7.1% and 6.4% of the total population, respectively. In women with an initially regular cycle, the rates of menstrual bleeding disorders were always below the average of all patients (spotting: 21%; breakthrough bleeding: 5.7%; amenorrhea: 5.4%). In 81.4% of the patients with absent withdrawal bleeding, it was reported that amenorrhea occurred in only one cycle. Intermenstrual bleeding was most common during the first treatment cycle; thereafter, its incidence decreased substantially (Fig. 1).

In 504 out of 817 patients (61.7%) who suffered from intermenstrual bleeding in the last two cycles before the start of the study, these symptoms were no longer present on Belara intake. Likewise, amenorrhea disappeared in 357 out of 400 women (89.3%) during study treatment. Intermenstrual bleeding and amenorrhea were newly diagnosed in 444 and 121 patients, respectively, corresponding to 25.0% and 5.5% of all patients not suffering from those symptoms before Belara intake.

Menstrual bleeding disorders occurred irrespective of the patient's age. The corresponding incidences ranged between 30.2% (age 19–28) and 34.8% (age <19). However, breakthrough bleeding and amenorrhea were reported more frequently in overweight women (14.4% vs. 6.4% and 9.6% vs. 6.1%, respectively). When analyzed by previous use of oral contraceptives, the overall frequencies of spotting, breakthrough bleeding and amenorrhea were similar in starters and switchers, with differences of 0.5–2.4%. During the first cycle of Belara intake, only the incidence of spotting in pill starters (20.7%) was above those of pill switchers (16.9%). In the further course of the study, this effect leveled out.

3.3.2. Dysmenorrhea

In 836 out of 1266 patients (66.0%) who suffered from dysmenorrhea in the last two cycles before the use of Belara, this symptom was no longer present during study treatment. On Belara intake, 13.0% of the women reported that dysmenorrhea was reduced, and only 0.7% complained about an increase in intensity. Out of 1324 patients without previous dysmenorrhea, 81 patients (6.1%) experienced this symptom for the first time while taking Belara.

Mild dysmenorrhea occurred more often in pill starters (19.9% vs. 14.7%), whereas severe dysmenorrhea was less frequent in this group compared to pill switchers (0.6% vs. 1.6%).

3.4. Effects on skin and hair

A considerable amount of women (85.6%) who used to suffer from spots or bad skin before taking Belara showed an improvement in these symptoms during the study. Out of the entire study population, a normal skin type was documented in 1678 patients (64.0%) during Belara treatment (baseline: 24.7%). A slightly greasy skin type was found in only 19.5% of the women (baseline: 35.5%). Likewise, the percentage of patients with greasy or very greasy skin decreased substantially from 26.6% at baseline to 2.3% on Belara intake (Fig. 2). The rate of dry skin conditions slightly improved to 9.1% (baseline: 12.8%). In patients with normal skin at baseline, no dermatological effects worth mentioning were observed, i.e., the skin type remained unchanged in 90% of the women in this group.

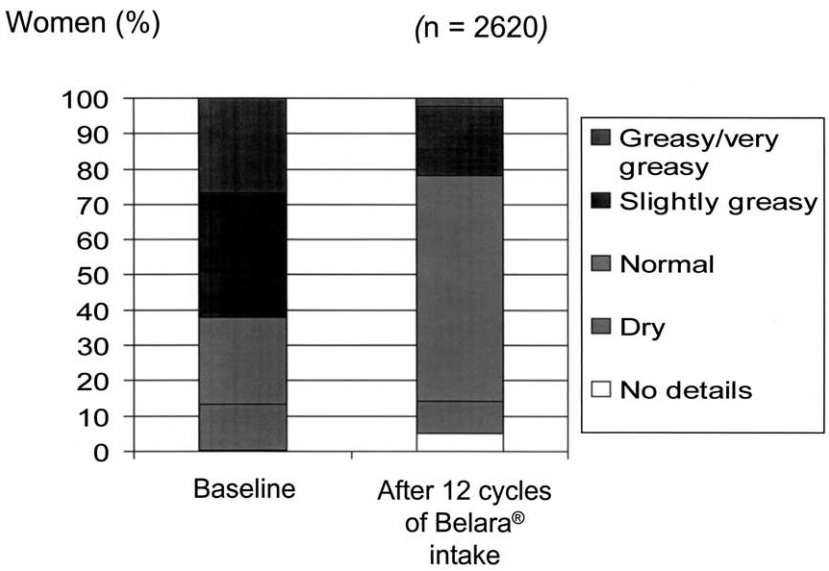

Fig. 2. Skin condition before and after 12 cycles of Belara® intake.

Beyond the improvement in skin condition, seborrheic characteristics of the hair type were also considerably diminished during Belara treatment. Thus, the percentage of women with greasy or very greasy hair decreased from 50.6% at baseline to 11.7% after 12 cycles of Belara intake. A normal hair type was documented in 2009 patients (76.7%; baseline: 41.3%), while the rate of women with dry hair remained nearly unchanged (5.5%; baseline: 7.6%). Along with the reduction in hair greasiness, there was also a decrease in daily hair washes. At baseline, 23.8% of all women preferred to wash their hair daily. After Belara intake, this was still the case for only 10.7% of all study participants.

3.5. Tolerability

3.5.1. Study withdrawal and compliance

A total of 346 patients (13.2%) stopped taking Belara before the end of the 12-month observation. Of these, 8.7% withdrew prematurely during the first two cycles, 52.3% stopped treatment during cycles 3–6 and 33.8% of the women withdrew during cycles 7–11. For the remaining 5.2%, no details on this point were available. It is important to note that 87 women (3.3% of all study participants) stopped Belara for nonmedical reasons, including 32 women (1.2%) who wanted to become pregnant. However, the main medical reasons for discontinuation of treatment were menstrual irregularities (28.9% of all withdrawals and 3.8% of all participants) and other common complaints during use of an OC, including headaches/migraine, weight gain, signs and symptoms of androgenization and breast pain (33.5% of all discontinuations and 4.4% of all women). It should be noted that 23.7%, 28.6% and 60.0% of the women who withdrew from the observation due to intermenstrual bleeding, amenorrhea and dysmenorrhea, respectively, already suffered from these symptoms before taking Belara.

Compliance data were available for a total of 2375 patients (90.6%). Of these, 205 women (7.8% of all study participants) stated irregularities. The intake mistakes most commonly occurred in the second (22.9%) and third treatment cycle (18.0%). During the further course of the study, the number of intake mistakes continuously decreased. More than half (60.5%) of these women forgot to take Belara once, a further quarter (25.4%) missed Belara intake for several times.

3.5.2. Adverse events

Beyond bleeding disorders and dysmenorrhea, 301 patients (11.5%) experienced further new symptoms or further symptoms with increased intensity (adverse events) during study treatment (Table 2). In 85.4% of the women with new or intensified symptoms, only one adverse event was found, whereas 13.0% and 1.7% recorded two and three different adverse events, respectively. However, with longer duration of Belara intake, the occurrence of adverse events became

Table 2
Incidence of adverse events[a] during Belara® intake (n = 2620)

Adverse event	Number of patients (% of total)
Breast pain	120 (4.6)
Migraine/headache	72 (2.7)
Gastrointestinal disorder	23 (0.9)
Weight gain	23 (0.9)
Depressed state	21 (0.8)
Tiredness	16 (0.6)
All other adverse events	(< 0.5)

[a] An adverse event is defined as a symptom that newly occurred or intensified during the observation period.

Table 3
Weight changes after 12 cycles of Belara® intake vs. age

Weight	% Women			
	Age <19 (n = 672)	Age 19–28 (n = 1184)	Age 29–38 (n = 622)	Age ≥39 (n = 124)
Loss >2 kg	3.0	5.5	5.6	2.4
Loss 1–2 kg	15.8	21.7	21.4	16.9
Unchanged	25.2	25.3	23.6	24.2
Increase 1–2 kg	37.8	31.4	33.3	43.6
Increase >2 kg	13.4	7.4	7.1	6.4
Not stated	4.9	8.7	9.0	6.4

less frequent. It was reported that 113 adverse events (32.3%; pill starters: 43.2%; pill switchers: 27.2%) were evaluated as mild, 34.6% as moderate and a severe intensity was stated for only 82 adverse events (23.4%; pill starters: 16.2%; pill switchers: 26.8%). For the remaining 34 adverse events (9.7%), details were missing.

The vast majority of women (78.8%) did not experience major weight changes during Belara treatment, i.e., loss or increase in weight of more than 2 kg. Further details on this point are shown in Table 3.

At the end of the eighth intake cycle, one case of venous thromboembolism (thrombosis in the left thigh) was discovered, leading to premature withdrawal of Belara. Nevertheless, no serious adverse event had been documented during the 12-month observation period.

3.5.3. Changes of symptoms on Belara intake

Migraine/headache, breast pain and depressed state are common complaints in daily gynecological practice. Most of the women suffering from at least one of these symptoms prior to study treatment reported that those complaints disappeared during Belara treatment (Fig. 3).

3.5.4. General assessment of tolerability

At the end of the observation period, the overall tolerability of Belara was scored both by the investigator and the patient as "very good," "good," "medium" or "poor." As a result, almost 85% of the women and more than 90% of the investigators stated the tolerability to be "very good" or "good" ("very good": patients 50.3%, investigators 56.3%; "good": patients 34.5%, investigators 34.6%). Only a few women and investigators assessed the tolerability to be moderate (patients: 5.9%; investigators: 4.8%) or poor (patients: 4.4%; investigators: 1.4%). For the remaining 4.9% of patients (investigators: 2.9%), no data were available. Correspondingly, 76.4% of the women expressed the definite wish to continue with Belara treatment even after completion of the 12-month observation period.

4. Discussion

This 12-cycle observational evaluation provides efficacy and tolerability data on the long-term everyday use of chlormadinone acetate 2.0 mg/ethinylestradiol 0.03 mg (Belara). The study population profile (starters and switchers, age distribution, proportion of smokers and nonsmokers) was generally typical of oral contraceptive users in Germany. This is important to obtain a reliable picture of the general female Belara user. A noninterventional design was used, thus reflecting routine gynecological practice.

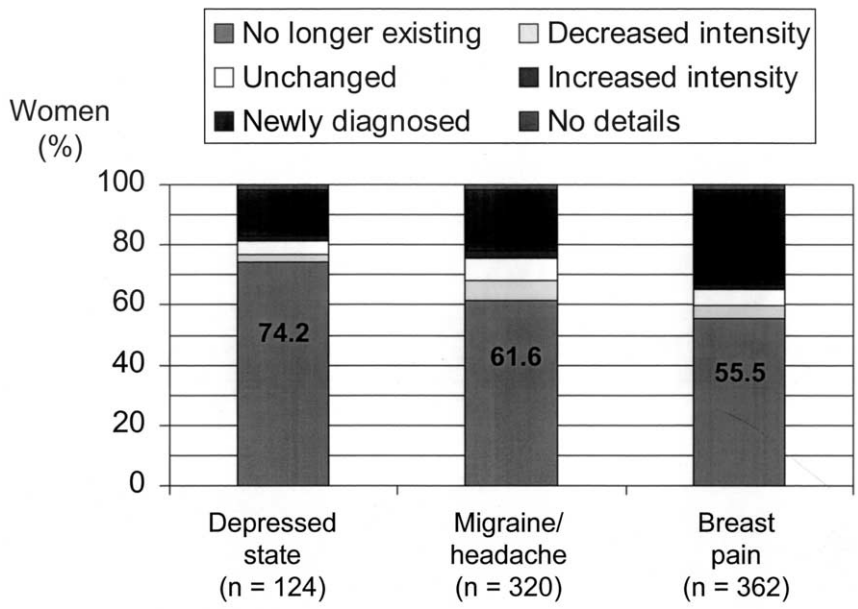

Fig. 3. Changes in depressed state, breast pain and migraine/headache after 12 cycles with Belara® treatment.

4.1. Contraceptive efficacy

The Pearl index—the number of pregnancies per 100 women-years of treatment—is a standard way of calculating the efficacy of contraceptives. This long-term postmarketing study confirms the reliable contraceptive efficacy of Belara, as evidenced by the unadjusted Pearl index of 0.44. However, 9 out of 10 pregnancies can be considered as user failures (noncompliance with recommendations for OC use), resulting in an adjusted Pearl index of 0.04. The contraceptive efficacy of Belara as measured by the Pearl index compares favorably to that of other OCs containing 0.03–0.035 mg EE, which have reported Pearl indices between 0 and 1.2 [13–16].

4.2. Effects on androgen-related disorders

A common complaint in daily gynecological practice are androgen-related disorders. Since hormonal imbalance is a key factor in the etiology of androgen-related skin and hair changes, OCs with anti-androgenic properties have proved to be a useful approach to minimize these effects [4,5]. The majority of women suffering from acne show a two- to threefold elevated activity of 5_{α}-reductase type I [17]. The latter converts testosterone into its more active compound, dihydrotestosterone, which stimulates the sebaceous glands. The CMA present in Belara is an inhibitor of 5_{α}-reductase type I and binds competitively with androgens thus downregulating the number of androgen receptors [7,8]. Indeed, several publications have documented positive effects of CMA on clinical manifestations of acne, seborrhea, alopecia and hirsutism [4,7,8]. The beneficial effects of CMA are supplemented by the EE component. EE reduces ovarian and adrenal synthesis of androgens and androgen precursors [18–20] and increases testosterone-binding SHBG (sex hormone-binding globuline) as well, thus leading to a reduced amount of free, biologically active testosterone [21]. In contrast to other progestogens derived from the 19-nortestosterone series, CMA does not counteract the favorable estrogenic influence [22].

As expected, the results of the present observation confirm the pronounced anti-androgenic properties of the CMA-containing OC Belara. More than 80% of all women with skin problems prior to the study reported substantial beneficial effects during Belara treatment. Likewise, the number of women with greasy or very greasy hair decreased by more than 75% after 12 cycles of Belara intake. Worret and colleagues compared the efficacy of EE/CMA (Belara) with a levonorgestrel (LNG)-containing combined OC (Microgynon) for the treatment of mild to moderate papulopustular acne of the face [23]. From study admission to cycle 12, deterioration rates of comedonal acne were significantly higher in the EE/LNG (9.1%) than in the EE/CMA group (2.8%), thus underscoring the anti-androgenic benefits of Belara as well.

4.3. Cycle control

Adequate cycle control is an important factor for the acceptance of an oral contraceptive, and problems with cycle control are probably the single most important reason for OC discontinuation [24]. More than 60% and almost 90% of the women who previously experienced intermenstrual bleeding or amenorrhea, respectively, reported that these symptoms completely disappeared on Belara intake. Out of the total study population, more than two thirds of all patients did not experience any bleeding disorder during the observation period. For the remaining patients, a consistent reduction in the prevalence of bleeding problems has been demonstrated with continued Belara use. These data are comparable to other published results with monophasic OCs [25–27].

Dysmenorrhea is a further common menstrual cycle disturbance causing discomfort in women. In almost two thirds of all patients who previously suffered from dysmenorrhea, this symptom was no longer present during Belara treatment. Studies have shown that about 60% of all teenage girls report dysmenorrhea and up to 14% miss school days because of this kind of complaint [28]. Women and adolescent girls may benefit from that reduction in symptoms of dysmenorrhea when taking the oral contraceptive Belara, allowing a more normal lifestyle.

4.4. Adverse events

Adverse events commonly associated with OCs, such as breast tenderness, migraine/headache, depressed state, tiredness, weight gain and gastrointestinal disorders, are often likely to prompt premature OC discontinuation [24]. In the course of the postmarketing study, only 15% of all women experienced at least one of these disorders as a new complaint or as a symptom with increased intensity. It is important to note that the frequency of these adverse events decreased with the duration of Belara use. Among those women who experienced migraine/headache, breast pain or a depressed state previously to the study, these complaints even disappeared or improved in well over two-thirds of them on Belara intake. Weight gain is another matter of considerable concern to oral contraceptive users. In the vast majority of women, Belara produced no or only small changes in weight. Correspondingly, Zahradnik and colleagues reported that the CMA-containing OC has no appreciable impact on appetite [12].

Among other reasons, the increased risk of VTE with higher doses of EE has contributed to the trend of lowering the concentration of EE in OCs. Indeed, the risk for VTEs has decreased with decreasing doses of hormones in OCs. For VTEs, the observed relative risk was reported to be lower with OCs containing <0.05 mg of EE compared to OCs containing ≥ 0.05 mg of EE [29,30]. In the present observation, only one case of thrombosis in the left thigh occurred, leading to premature withdrawal of Belara. The

results of a phase III study which enrolled a total of 21,820 women confirm the low incidence of thromboembolic events with the CMA-containing OC. During the six-cycle treatment period, only one case of a thromboembolic event (pulmonary embolism) and one case of superficial leg vein thrombosis were diagnosed, both recovering with appropriate treatment [12].

In conclusion, this observational study confirms the reliable 1-year contraceptive efficacy, high cycle stability and excellent tolerability profile during the use of Belara. Furthermore, additional benefits on skin and hair underscore the well-known anti-androgenic properties of the CMA-containing OC.

Acknowledgment

This study was conducted and sponsored by Grünenthal GmbH, Germany. The authors would like to thank all of the 435 gynecologists and Grünenthal staff who participated in the study.

References

[1] Rabe T, Runnebaum B. The future of oral hormonal contraception. In: Rabe T, Runnebaum B, editors. Fertility control. Berlin, Heidelberg, New York: Springer, 1999. p. 73–89.
[2] Mall-Haefeli M. Die Wirkung der Androgene auf das Zyklusgeschehen. In: Loch E, Schramm G, editors. Chlormadinonacetat bei Androgenisierungserscheinungen. Stuttgart, New York: Schattauer, 1995. p. 43–55.
[3] Elstein M, Furniss H. The fiction of an ideal contraceptive. Adv Contracept 1996;12:129–38.
[4] Kaiser E. Action of a new hormonal contraceptive (Neo-Eunomin®) on androgenisation of the skin in women. Geburtsh U Frauenheilkunde 1984;44:651–5.
[5] Carlborg L. Cyproterone acetate versus levonorgestrel combined with ethinylestradiol in the treatment of acne. Acta Obstet Gynecol Scand 1986;134:29–32.
[6] Kuhl H. Chemie und pharmakologie von chlormadinonacetat. In: Loch EG, Schramm G, editors. Chlormadinonacetat bei Androgenisierungserscheinungen. Stuttgart, New York: Schattauer, 1995. p. 1–12.
[7] Breckwoldt M, Wieacker P. Hirsutismus. In: Bettendorf G, Breckwoldt M, editors. Reproduktionsmedizin. Stuttgart: Fischer, 1989. p. 483–7.
[8] Breckwoldt M, Zahradnik HP, Wieacker P, Hirsutism. In: Orfanos CE, Happle R, editors. Hair and hair diseases. Berlin: Springer-Verlag, 1990. p. 777–89.
[9] Luderschmidt C. Akne der Frau—eine interdisziplinäre Herausforderung. In: Loch EG, Schramm G, editors. Chlormadinonacetat bei Androgenisierungserscheinungen. Stuttgart, New York: Schattauer, 1995. p. 57–76.
[10] Kuhl H. Oral Contraceptives and androgenic symptoms. Geburtsh u Frauenheilk 1999;59:191–8.
[11] Basdevant A, Conard J, Pelissier V, et al. Haemostatic and metabolic effects of lowering the ethinylestradiol dose from 30 mg to 20 mg in oral contraceptives containing desogestrel. Contraception 1993;48: 193–204.
[12] Zahradnik HP, Goldberg J, Andreas JE. Efficacy and safety of the new antiandrogenic oral contraceptive Belara®. Contraception 1998; 57:103–9.
[13] Speroff L, De Cherny A. Advisory board for the new progestin. Evaluation of a new generation of oral contraceptives. Obstet Gynecol 1993;81:1034–47.
[14] Corson SL. Efficacy and clinical profile of a new oral contraceptive containing norgestimate. Acta Obstet Gynecol Scand 1990;152:25–31.
[15] Physicians' Desk Reference. 54th ed. Montvale, NJ: Medical Economics, 2000. p. 2086, 2168–91.
[16] Runnebaum B, Rabe T. Gynäkologische endokrinologie. Berlin, Heidelberg, New York: Springer, 1994. p. 412–53.
[17] Sansone G, Reisner RM. Differential rates of conversion of testosterone to dihydrotestosterone in acne and in normal human skin—possible pathogenetic factors in acne. J Invest Dermatol 1971;56: 366–72.
[18] Mc Kenna TJ. The use of anti-androgens in the treatment of hirsutism. Clin Endocrinol 1991;35:1–3.
[19] Dieben T, Vromans L, Theeuwes C, et al. The effects of CRT-24, a biphasic oral contraceptive combination, compared to Diane-35 in women with acne. Contraception 1994;50:373–82.
[20] Redmond GP, Olson WH, Lippmann JS, et al. Norgestimate and ethinylestradiol in the treatment of moderate acne vulgaris. Obstet Gynecol 1997;89:615–22.
[21] Lucky AW, Henderson TA, Olson WH, et al. Effectiveness of norgestimate and ethinylestradiol in treating moderate acne vulgaris. J Am Acad Dermatol 1997;37:746–54.
[22] Winkler H. Chlormadinonacetat: Stoffwechsel und Hämostase. In: Loch EG, Schramm G, editors. Chlormadinonacetat bei Androgenisierungserscheinungen. Stuttgart, New York: Schattauer, 1995. p. 17–24.
[23] Worret I, Arp W, Zahradnik HP, et al. Acne resolution rates: results of a single-blind, randomized, controlled, parallel phase III trial with EE/CMA (Belara®) and EE/LNG (Microgynon®). Dermatology 2001;203:38–44.
[24] Rosenberg MJ, Waugh MS. Oral contraceptive discontinuation: a prospective evaluation of frequency and reasons. Am J Obstet Gynecol 1998;179:577–82.
[25] Rebar RW. Combination oral contraceptives. Curr Ther Endocrinol Metab 1997;6:275–80.
[26] Dunson TR, Mc Laurin VL, Aguayo EL, et al. A multicenter comparative trial of triphasic and monophasic, low-dose combined oral contraceptives. Contraception 1993;4:515–25.
[27] Fotherby K. Twelve years of clinical experience with an oral contraceptive containing 30 μg ethinylestradiol and 150 μg desogestrel. Contraception 1995;51:3–12.
[28] Klein JR, Litt IF. Epidemiology of adolescent dysmenorrhea. Pediatrics 1981;68:661–4.
[29] WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. Lancet 1996;348:498–505.
[30] Vessey MP. Epidemiologic studies of oral contraception. Int J Fertil 1989;34(Suppl):64–70.