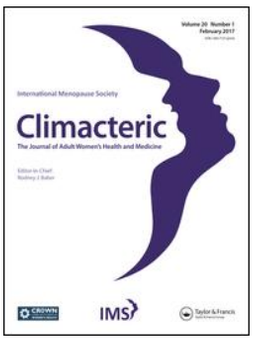

Climacteric

ISSN: 1369-7137 (Print) 1473-0804 (Online) Journal homepage: https://www.tandfonline.com/loi/icmt20

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To cite this article: R. E. Nappi, M. Kotek, A. Brešťanský, N. Giordan & E. Tramentozzi (2020): Effectiveness of hyaluronate-based pessaries in the treatment of vulvovaginal atrophy in postmenopausal women, Climacteric, DOI: 10.1080/13697137.2020.1754386

To link to this article: https://doi.org/10.1080/13697137.2020.1754386

CLIMACTERIC
https://doi.org/10.1080/13697137.2020.1754386

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ORIGINAL ARTICLE

Effectiveness of hyaluronate-based pessaries in the treatment of vulvovaginal atrophy in postmenopausal women

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ABSTRACT

Objectives: This study aimed to assess the efficacy and safety of hyaluronic acid-based vaginal pessaries (Hydeal-D) in the treatment of vulvovaginal atrophy (VVA).

Study design: The study was a prospective, multicenter clinical investigation of VVA topical treatment in 40 postmenopausal women. Patients applied one Hydeal-D pessary every 3 days for 3 months.

Main outcome measures: The primary endpoint was the amelioration of VVA signs after treatment, evaluated by measuring the change from baseline of the Vaginal Health Index (VHI) score. Secondary endpoints included the evaluation of other VVA-related signs and symptoms, safety, and patient-reported and clinician-reported satisfaction and treatment tolerability.

Results: The 3-month treatment with Hydeal-D vaginal pessaries showed efficacy for all analyzed endpoints. Improvement exceeded threshold values of VVA diagnosis, sexual dysfunction, and distress, confirming clinically relevant amelioration of VVA symptoms. Changes from baseline conditions confirmed significant improvement of all parameters including the VHI, vaginal pH, patients' perception of VVA symptoms, sexual function, and vaginal maturation. Patients' overall satisfaction was very high after 1 month of treatment and increased further after 3 months. No severe adverse events were reported.

Conclusions: Significant amelioration of VVA-related signs indicates that Hydeal-D vaginal pessaries are an effective, safe, and well-tolerated non-hormonal therapeutic option for VVA in postmenopausal women.

ARTICLE HISTORY
Received 29 October 2019
Revised 2 March 2020
Accepted 7 April 2020
Published online 12 May 2020

KEYWORDS
Vulvovaginal atrophy; hyaluronic acid; vaginal pessaries; menopause; vaginal dryness

Introduction

Vulvovaginal atrophy (VVA) is a distressing medical condition which is an integral part of the genitourinary syndrome of menopause[1]. VVA occurs in about 50% of postmenopausal women because of ovarian exhaustion and aging phenomena[2,3]. Other hypoestrogenism states associated with postpartum, oophorectomy, chemotherapy, and use of antiestrogen medications may lead to VVA symptoms[4]. Some risk factors such as obesity, diabetes mellitus, smoking, no vaginal delivery, and decreased sexual activity have also been associated with VVA[5]. The most common symptoms include vaginal dryness and dyspareunia followed by irritation, burning, itching, discharge, urinary discomfort, and bleeding with intercourse[6]. The burden of symptoms on women's daily living is associated with typical signs detected during a physical examination[7] and with laboratory tests, such as pH and the maturation index[1,8]. Despite the increasing number of elderly women carrying the VVA condition, the rate of effective treatment is still unsatisfactory[9] and recent data indicate a delay in the clinical management of VVA symptoms[10]. Health-care providers should be proactive, given the plethora of options, including lifestyle modification and hormonal treatments as well as non-hormonal approaches, such as lubricants and moisturizers, and non-drug therapies[11]. Contraindications to estrogen use, fears of hormones, potential side effects of treatments, and attitudes of postmenopausal women to VVA[9] explain the wide use of lubricants and moisturizers alone or in association with other options[12]. Both osmolality and pH are important characteristics for lubricants and moisturizers giving temporary relief to vaginal dryness and rehydrating vaginal tissues over time, respectively[13].

A subgroup of vaginal moisturizers containing hyaluronic acid (HA), a high-molecular-weight polysaccharide, have

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Supplemental data for this article can be accessed here.

been listed as one of the most effective strategies to help women with VVA symptoms who cannot or do not want to use hormones[14]. Indeed, HA represents a major component of the extracellular matrix that can bind large amounts of water, because of its particular molecular structure and properties[15]. The properties of HA preparations are determined by their molecular weight, concentration, and molecular modifications, which largely determine their density, permeability, and mechanical properties. Due to the ubiquitous expression of HA in the human body and its biocompatibility, HA formulations have been widely used in a variety of medical applications[16].

Recently, vaginal pessaries containing Hydeal-D (Fidia Farmaceutici, Abano Terme, Italy), a HA ester characterized by strong hydrating properties, have been developed and registered as Hyalo Gyn/Hyalofemme vaginal ovules (Class 2A medical device). Hydeal-D vaginal pessaries are non-sterile, glyceride-based, solid preparations for single-dose vaginal administration, containing 0.2% Hydeal-D, indicated for the treatment of vaginal dryness of varying origin and in the natural healing process of friction-induced microlesions in the vaginal mucosa. The principal component, Hydeal-D, has been successfully employed in a gel formulation to reduce vaginal dryness[17] and to prevent sexual dysfunction in postmenopausal breast cancer survivors with VVA[18]. The Hyalo Gyn/Hyalofemme vaginal ovules are made from 90% vegetal glycerides, which create a wax-like texture and ensure low friction when inserting and removing the ovules through the VVA-affected vaginal mucosa.

The overall aim of this prospective, multicenter clinical investigation was to assess the efficacy and safety of Hydeal-D vaginal pessaries in the treatment of VVA in postmenopausal women. The primary objective was to evaluate the efficacy on vaginal health measured by the Vaginal Health Index (VHI) (vaginal elasticity, fluid volume, pH, mucosa epithelial integrity, and moisture)[19] after 3 months of treatment. Secondary aims included the evaluation of other VVA-related signs and symptoms, safety, and patient-reported and clinician-reported satisfaction and tolerability of the treatment.

Materials and methods

Study design

The present study was a prospective, multicenter, single-arm, open-label, 3-month clinical investigation exploring the efficacy and safety of a topical treatment on postmenopausal women with VVA attending two centers in Slovakia; the investigation lasted from November 2017 to April 2018 (first patient, first visit to last patient, last visit). The study was carried out in compliance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practices International Conference on Harmonization Guidelines, and the ISO14155 Clinical investigation of medical devices for human subjects – Good Clinical Practice. The study was approved by the local ethics committees (Approval no. CIV-SK-17-09-021684) and registered on www.clinicaltrials.gov (identifier: NCT03557398). All subjects provided signed informed consent.

Patients

During a screening visit, the following inclusion and exclusion criteria were addressed. Inclusion criteria were: postmenopausal state of the patients ($\geq$12 months since last spontaneous menstrual period, or 6 months of spontaneous amenorrhea with serum FSH levels >40 IU/l, or surgically postmenopausal for >6 months), age from 45 to 75 years, vaginal pH $\geq$ 5, VHI $\leq$ 15[20], and at least one of the symptoms of VVA (vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, vaginal pain associated with sexual activity), assessed as moderate to severe.

Patients were excluded if they were treated with any kind of non-hormonal product for VVA in the week preceding the screening visit or with oral or topical hormonal products within 1 month before the screening visit. Other exclusion criteria were the presence of clinical signs of vaginal infections or a history of vulvovaginal contact allergy. Patients who were not sexually active or presented acute hepatopathy, embolic disorders, severe primary disease of the kidney and hematopoietic system, history of malignant tumors, or a hypersensitivity to any component of the Hydeal-D vaginal pessaries were also excluded from the study.

Patients enrolled in the study were asked not to apply any other vaginal topical hormonal product within 1 month and/or a non-hormonal product within 1 week, prior to starting the application of Hydeal-D pessaries.

Intervention

Hydeal-D vaginal pessaries were applied once every 3 days to a total of 12 consecutive weeks (3 months) and patients were visited at baseline (V1), 4 weeks post treatment (V2), and 12 weeks post treatment (V3).

At each visit, the following clinical evaluations were performed: VHI, vaginal pH, patient perception of vulvovaginal symptoms, and assessment of sexual function. V1 and V3 furthermore included the collection of a vaginal smear for the cytological evaluation of the Vaginal Maturation Index (VMI). V2 and V3 additionally recorded the patient's overall satisfaction and local tolerability of the product at the application site, as well as the occurrence of any adverse events (AEs). Concomitant medications taken by the patient were recorded at all visits.

Endpoint assessments

The primary endpoint of the clinical investigation was the amelioration of the vaginal signs associated with VVA, evaluated by measuring the change from baseline of the average VHI score[19] after 3 months of treatment. During the visit, the investigator performed a quantitative assessment of vaginal health evaluating vaginal elasticity, fluid volume, pH, epithelial mucosa integrity, and moisture, on a scale ranging from 1 (none) to 5 (excellent), with a total cut-off score $\leq$ 15. The VHI assessment was performed, as a secondary endpoint, also after 1 month of treatment. Other secondary endpoints, evaluated as changes from baseline to 1 and 3 months,

included the following: vaginal pH measured by inserting a pH test strip (pH 4.0–7.0; Merck KGaA, Darmstadt, Germany) in the upper wall of the vagina (patients were scored in subgroups according to their pH, considering that pH 5–5.49 indicates mild atrophy, pH 5.5–6.49 moderate atrophy, and pH > 6.5 severe atrophy[20]); total score of patient's perception of VVA-associated symptoms (dryness, irritation/itching, soreness, dysuria, dyspareunia), individually reported on a 4-point scale according to the severity of perceived symptoms (0 = absent, 1 = mild, 2 = moderate, 3 = severe), ranging from 0 to 15, as previously published[21,22]; sexual function assessed through the Female Sexual Function Index (FSFI) questionnaire, a mean weighed score based on questions related to patients' sexual sensations focused on six domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) and scored on a 5-point scale (0 = no sexual activity, 1 = never/very low, 5 = always/very high) (the cut-off score for the diagnosis of female sexual dysfunction is ≤26.55[23]); and personal distress associated with sexual dysfunction assessed through the Female Sexual Distress Scale – Revised (FSDS-R), a 13-item questionnaire where the threshold for female sexual distress corresponds to an overall score ≥ 11[24]. A further secondary endpoint included the change of the VMI from baseline to 3 months of treatment. The VMI was obtained from the cellular count of vaginal smears, and quantified as the relative proportion of three types of vaginal epithelium cells (parabasal, intermediate, and superficial) indicating the degree of tissue estrogenization[25]. The samples were fixed, stored, and sent to a centralized laboratory (Cytophatos, spol. s.r.o., Bratislava, Slovakia) for staining (Papanicolau technique) and analysis. The VMI was calculated according to the following equation: VMI = [1 (% superficial cells)] + [0.6 (% intermediate cells)] + [0.2 (% parabasal cells)]. Other endpoints were: the patient's global assessment of overall satisfaction (PTGA) scored on a 4-point scale (0 = dissatisfied or very dissatisfied, 1 = moderately satisfied or satisfied, 2 = very satisfied, and 3 = greatly satisfied); local tolerability of the product at the application site, evaluated after 1 and 3 months of treatment by both the clinician and the patient using a 5-point scale (1 = excellent [no reaction], 2 = good [small reaction that spontaneously resolved], 3 = moderate [reaction tolerated with difficulty by the subject], 4 = poor [reaction needing interruption of treatment], 5 = bad [serious reaction]); and safety of the treatment, evaluated by collecting all AEs during the study[26].

Statistical analysis

The null hypothesis was that the lower limit of the 97.5% confidence interval of the VHI total score change from baseline to 3 months of follow-up was less than 20%. Under the formulated hypotheses, the study required a sample size of 37 patients to achieve a power of 90% and a level of significance of 5% (one-sided), assuming the standard deviation of the differences to be 40%. Assuming a dropout of no more than three subjects, it was estimated to recruit 40 postmenopausal women with VVA.

Subjects' demographics and baseline characteristics were summarized using descriptive statistics. Frequencies and percentages were used for qualitative variables; mean ± deviation, minimum and maximum value (range), median, and first and third quartiles (interquartile range) were used for quantitative variables.

Differences in scores before and after treatment were calculated and the Shapiro–Wilk test was used to verify the normality of their distribution. A paired Student's *t*-test was used to test differences in scores with a normal distribution, and the Wilcoxon signed-rank test used for non-normal distributions and for non-parametric values. All statistical tests were considered significant if inferior to 0.05 ($p < 0.05$).

Results

Forty postmenopausal women (mean age, 57.1 ± 5.9 years) diagnosed with VVA were enrolled in the study, and all patients completed the study. Demographics and baseline characteristics are summarized in Table 1.

Scores and percentage changes in overall VHI, the primary endpoint of this study, are shown in Figure 1 and Supplementary Table 1. The mean VHI total score increased significantly ($p < 0.0001$) from 9.2 ± 2.74 at baseline to 18.4 ± 3.32 at 12 weeks of treatment (Figure 1). The percentage change from baseline (111.9 ± 55.24% after 3 months) by far exceeded the expected mean VHI increase of 20% set for the sample size calculation. Significance of the VHI percentage change from baseline to month 3 was confirmed by repeated-measures analysis of variance ($p < 0.0001$) considering the baseline score as a covariate and thus confirming the efficacy of Hydeal-D over time. The single VHI item category changes from baseline considerably increased during 1 and 3 months of treatment ($p < 0.0001$) and at least 90% of patients improved in ≥1 item category after 3 months (Supplementary Table 1). The number of patients with an overall VHI score ≤ 15, the threshold value for VVA diagnosis, decreased from 100% at screening and baseline visits to 50% and 20% at the 4-week and 12-week follow-up visits, respectively.

The analysis of the secondary endpoints showed that vaginal pH, which is an indicator of VVA, significantly improved both after 1 and 3 months of Hydeal-D treatment ($p < 0.0001$, signed-rank test) The subgroup of patients with vaginal pH < 5 increased from no patient at baseline to 11 patients (27.5%) and 21 patients (52.7%) after 1 and 3 months of treatment, respectively. Accordingly, the number

Table 1. Patients' demographics and baseline characteristics (*N* = 40).

Variable	*Mean ± standard deviation*	*Median (minimum, maximum)*	*Quartiles (25%, 75%)*
Age (years)	57.1 ± 5.90	56.5 (48.0, 69.0)	(52.0, 61.5)
Body mass index (kg/m^2)	26.2 ± 3.77	26.4 (16.6, 32.4)	(24.3, 28.8)
Height (cm)	164.9 ± 5.04	164.0 (157.0, 178.0)	(160.5, 169.0)
Weight (kg)	71.4 ± 10.62	73.0 (48.0, 89.0)	(64.0, 80.0)

of patients in the subgroup with pH > 6.49 decreased from 14 patients (35%) at baseline to eight patients (20%) at month 1 and three patients (7.5%) at month 3 (Figure 2 and Supplementary Table 2). Patients with a pH score improvement of at least one grade numbered 27 (67.5%) after 1 month and 36 (90%) after 3 months of treatment (Figure 2 and Supplementary Table 2). Only three patients with pH > 6.49 showed no decrease in pH after 3 months but displayed improvement in the other signs and symptoms of VVA.

The mean total score for patient's VVA symptom perception improved significantly ($p < 0.0001$), decreasing from

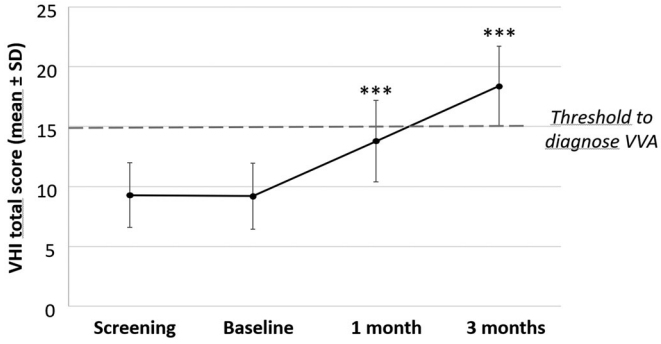

Figure 1. Effect of Hydeal-D vaginal pessaries on the Vaginal Health Index (VHI) of postmenopausal women. VHI scores, expressed as mean ± standard deviation (SD), evaluated in 40 patients at screening, at baseline, and at 1 and 3 months of treatment are presented. Significance levels were calculated at 1 and 3 months of treatment compared to baseline (***$p < 0.0001$, signed-rank test) and confirmed by repeated-measures analysis of variance. VVA, vulvovaginal atrophy.

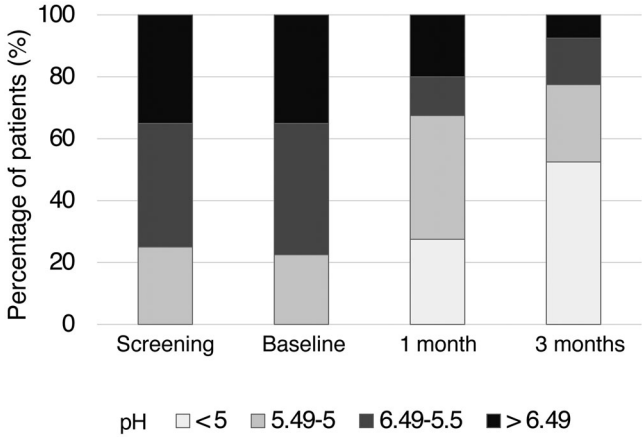

Figure 2. Significant decrease in vaginal pH in postmenopausal women treated with Hydeal-D vaginal pessaries. Vaginal pH changes were assessed in 40 postmenopausal women at screening, at baseline, and after 1 or 3 months of treatment with Hydeal-D. The percentage of patients in four different pH subgroups at all visits is reported. Significance levels were calculated by signed-rank test at 1 and 3 months compared to baseline. Differences were considered significant with $p < 0.05$. ***$p < 0.0001$.

7.0 ± 2.45 at baseline to 2.5 ± 2.09 and 0.5 ± 0.85 after 1 and 3 months, respectively (Table 2). The analysis of single items showed a significant reduction ($p < 0.0001$) during both 1 and 3 months of treatment. Patient's perception of vaginal dryness improved in at least one score in 97.5% of patients (Table 3).

Results from the FSFI questionnaire showed that the patients' perception of sexual function improved significantly after 1 month ($p = 0.0142$) and 3 months ($p < 0.0001$) of using the Hydeal-D vaginal pessaries. The FSFI mean full scale score value of 22.5 at baseline increased to 24.7 at 1 month and to 28.5 at 3 months. A mean full scale value lower than 26.55, the female sexual dysfunction cut-off value, was reported by 67.5% of patients at baseline and decreased to 47.5% and 30% after 1 month and 3 months, respectively. Female sexual distress was reduced from 14.8 at baseline to 13.6 ($p = 0.0963$) after 1 month and to 8.6 ($p < 0.0001$) after 3 months of treatment, with an increase in the number of patients reporting values lower than the cut-off value for personal distress of 11, from 47.5% at baseline to 55% and 70% of at 1 month and 3 months, respectively (Supplementary Table 3).

Furthermore, the mean VMI increased significantly ($p = 0.0022$) from 54.6 at baseline to 62.8 at month 3. Interestingly, the increase in the percentage of superficial cells was not significant during 3 months of treatment, whereas a significant improvement was observed in parabasal cells (decrease from 31.3% at baseline to 14.8% at month 3; $p = 0.0004$). For intermediate cells, the increase from 51.8% at baseline to 63.5% at month 3 was also significant ($p = 0.0187$) (Supplementary Table 4).

Patients' overall satisfaction was very high, as 25 patients (62.5%) were greatly satisfied and 14 patients (35.0%) were satisfied to very satisfied with the treatment after 3 months. Only one patient (2.5%) was dissatisfied or very dissatisfied after 3 months of treatment. Thirty-seven patients (92.5%) positively appreciated study treatment already after 1 month and the number of patients with higher satisfaction grade further increased to month 3 (Supplementary Table 4).

Local tolerability of the product at the application site was evaluated as excellent (no reaction) by 100% of the investigators in all patients and at all time points.

Excellent local tolerability was reported by all patients at both follow-up visits, except for two patients presenting vulvovaginal erythema reported as an AE and who evaluated local tolerability as good – one patient at month 1 and the second patient at month 3. During the study, three AEs were reported in two patients; two AEs were mild vulvovaginal erythema, the first was related and the second possibly related to the study device, according to the investigators.

Table 2. Summary statistics for the total score of patients' perception of vulvovaginal symptoms ($N = 40$).

	Total score			
Visit	*Mean ± standard deviation)*	*Median (minimum, maximum)*	*Quartiles (25%, 75%)*	p-*Value (statistical test)*
V1 (baseline)	7.0 ± 2.45	7.0 (3.0, 13.0)	(5.0, 8.5)	
V2 (4 weeks)	2.5 ± 2.09[a]	2.5 (0.0, 7.0)	(0.5, 4.0)	<0.0001 (Student's *t*-test)
V3 (12 weeks)	0.5 ± 0.85[a]	0.0 (0.0, 4.0)	(0.0, 1.0)	<0.0001 (Student's *t*-test)

Significance levels were calculated at V2 and V3 compared to V1 using the indicated tests.
[a]Significance comparing results to baseline levels; differences were considered significant with $p < 0.05$.

Table 3. Single symptom score change of patients' perception of vulvovaginal symptoms ($N = 40$).

Decrease ≥ 1 from baseline at visit 3 (12 weeks), n *(%)*					
Dryness	*Irritation/itching*	*Soreness*	*Dysuria*	*Dyspareunia*	p-*Value (statistical test)*
39 (97.5)[a]	38 (100)[a]	38 (100)[a]	21 (52.5)[a]	34 (85)[a]	<0.0001 (Student's *t*-test)

Significance levels were calculated at 4 and 12 weeks compared to baseline using the indicated tests.
[a]Significance comparing results to baseline levels; differences were considered significant with $p < 0.05$.

The third AE was reported as mild, and not related to the study device in one of the two patients who experienced vulvovaginal erythema. No severe AE was reported and no patient discontinued her participation due to an AE.

Discussion

The present prospective, multicenter clinical investigation demonstrated that 3-month treatment with the HA-based Hydeal-D vaginal pessaries was safe and effective in ameliorating postmenopausal VVA signs and symptoms. Improvement exceeded, in some patients, the thresholds for diagnosis of VVA and sexual dysfunction. Efficacy was confirmed by significant changes in all evaluated parameters: VHI, vaginal pH, patient perception of vaginal dryness, dyspareunia, irritation/itching, soreness, dysuria, sexual function and distress, and VMI. Interestingly, a statistically relevant improvement was observed already after 1 month of treatment, but an even more relevant clinical improvement was evident for some parameters at 3 months of treatment. Patients' overall satisfaction with the treatment was very high, and tolerability and safety were also high.

In spite of the severe impact on quality of life and sexual well-being of postmenopausal women, VVA is still greatly underdiagnosed and undertreated[3]. Due to the concerns related to hormonal-based topical treatments, non-hormonal vaginal strategies are widely used[27], with moisturizers showing some therapeutic effect[28]. Since the water-retaining capacity of vaginal tissues is decreased during menopause and HA is naturally excreted by vaginal tissues, HA-based preparations represent a promising strategy to correct hydration and improve clinical symptoms and signs related to VVA[17,18]. A previous prospective observational study[29] described an improvement of the mean VHI from 9.65 at baseline to 19.96 after 8 weeks of topical vaginal treatment with an HA-based liquid preparation, a finding similar to our present results. A placebo-controlled, short-term study[30] showed that daily use of Hydeal-D vaginal gel was more effective in reducing symptoms of VVA, whereas the safety and tolerability were similar in both treatment arms. When HA-based preparations were compared with local estrogen treatments, the results were mixed[17,31,32], but indicated that both treatments provided relief of vaginal symptoms, improved epithelial atrophy, decreased vaginal pH, and increased VMI. Interestingly enough, even though no head-to-head trials have been performed, the short-term trophic effect of HA-based Hydeal-D vaginal pessaries seems to be similar to that observed with other non-hormonal approaches, such as laser therapies[33,34] and even the use of serotonin reuptake inhibitors[35]. Thus, it seems likely that any strategies ameliorating discrete parameters of the functional anatomy of the vagina, such as vasodilation, collagenesis, and cellularity of the extracellular matrix, may be effective in treating VVA signs and symptoms. However, we are still in need of long-lasting and comparative data; most importantly, we lack a real decision-making algorithm to establish a tailored approach to women's expectations and to the type and severity of specific complaints associated with VVA[36].

Even the restoration of sexual function and the decrease of sexual distress with HA-based Hydeal-D vaginal pessaries is of note, given the high rate of sexual dysfunction associated with VVA[37].

The present study provides an overall evaluation of the multifactorial signs and symptoms of VVA ranging from objective measures of the vaginal morphology to subjective patient-reported symptoms and perception of sexual function. In addition, the global improvement of these numerous primary and secondary endpoints with a follow-up of 3 months further corroborates the study results. Limitations of this study include the absence of randomization and a control arm, as well as the fact that treatment was not blinded either for the investigator or for the patient. Indeed, the lack of a control arm and the lack of blinding do not allow one to exclude a placebo effect or the effect of other confounding factors from the observed improvements in VVA-associated symptoms.

In conclusion, this clinical investigation suggests that Hydeal-D vaginal pessaries could be a safe, well-tolerated, and effective non-hormonal therapeutic option for treatment of VVA in postmenopausal women, thus offering a further topical application choice for the treatment of this common condition in clinical practice. Future randomized controlled studies should be carried out to further confirm the results reported in the present study.

Potential conflict of interest No potential conflict of interest was reported by the authors.

Source of funding This study was funded by Fidia Farmaceutici SpA.

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