Veregen® ointment as a potential novel treatment for usual type vulval intraepithelial neoplasia: a single center randomised control study

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May 5, 2020

Abstract

Objective To compare the safety and efficacy of Veregen® ointment against placebo in the treatment of usual type vulvar intraepithelial neoplasia (uVIN). Design A Phase II randomised control trial. Setting A tertiary gynaecological oncology referral center. Population All women diagnosed with primary and recurrence uVIN. Methods Eligible patients were randomised to receive either Veregen® or placebo ointment (applied 3 times daily for 16 weeks), and were followed up at 2, 4, 8, 16, 32 and 52 weeks. Main outcome measures Outcome measures, recorded at 16 and 32 weeks, were histological (HR) and clinical (CR) response (as measured by [?]30% reduction in the sum of the longest diameter of all lesions when compared to baseline), toxicity and changes in quality of life and pain scores. Results 26 patients were randomised and all 13 patients who received Veregen(r) showed either complete (n=5) or partial (n=8) CR with a trend towards an improvement in baseline symptoms. In placebo group, 3 patients had complete CR, 2 had partial CR and 6 had stable disease. Patients in the Veregen(r) group showed a significant improvement in CR as compared to the placebo group (P=0.0026). There was no evidence of difference in HR and toxicity reported in both groups. Conclusion Our study indicates that Veregen application is safe and leads to at least a partial clinical resolution of uVIN lesions and symptoms improvement, thus warranting a phase III multi-centre RCT.

Tweetable abstract A randomised control study indicating that Veregen® ointment may be a novel treatment for uVIN.

Introduction

Usual type vulvar intraepithelial neoplasia (uVIN), a putative precursor lesion of VSCC, is associated with persistent high-risk HPV (HR-HPV) infection; predominantly, the HPV16 strain.[1,2] The condition primarily affects young women, with a peak age incidence of 30-49 years. In recent years, the incidence of VIN has increased by more than 3-fold.[3,4] Although the malignant progression of uVIN is significantly lower than that of cervical intraepithelial neoplasia (CIN),[5] typically of the order of 10%, unlike CIN, it often causes

debilitating symptoms such as pruritus, pain and sexual dysfunction. To date, effective medical treatment is still lacking,[6] and there is a compelling need for new medical treatments which could interrupt the natural history of uVIN.

Veregen® ointment, with epigallocatechin-3-gallate (EGCG) as its primary bioactive green tea polyphenol, has been proved to be safe and effective in eradicating genital warts,[7] a low-risk HPV-associated proliferative disorders. Here, we report findings from a Phase II randomised control feasibility study (EPIVIN) which evaluates the use of Veregen® ointment in the treatment of women with uVIN, a hyperproliferative disorders caused by high-risk HPV infection.

Methods

The study was designed as a Phase II, single-centre, double-blind, randomised control trial. Inclusion criteria were all women were [?] 18 years of age who presented with histologically proven uVIN on biopsy, either as primary or recurrence disease. All uVIN lesions must be measurable with at least one lesion that can be accurately measured in one dimension with longest diameter [?] 10mm. Patients with recurrence disease were treatment free for at least 12 weeks and must be able to provide a written consent to participate in the study. Exclusion criteria were patients suspected or histological proven invasive disease; pregnant, breast feeding or were trying to conceive; know allergies to any of Veregen(r) or placebo components; underlying immunosuppressive disease; unable to comply with protocol; severe liver dysfunction or chronic liver disease; unable to provide written consent. This study is approved by the East Midlands - Derby Research Ethics Committee with study number 13/EM/0398. All patients provided a written consent to participate in the study.

Patients who fulfilled the recruitment criteria were randomised 1:1 into receiving Veregen(r) (experimental) or a placebo ointment. Veregen(r) ointment, 10% EGCG concentration, and placebo were manufactured and supplied by MediGene AG, Germany. Patients were to apply ointment thrice daily for 16 weeks, and the frequency of application was recorded in a diary. Follow up were scheduled at two weeks (telephone call), 4, 8, 16, 32 and 52 weeks after starting treatment. Baseline biopsy for histological diagnosis was obtained prior to treatment and at 16 and 32 weeks after treatment. Recruitment to the trial was scheduled for 24 months. The study protocol is included in the supplementary information.

The primary objective was to evaluate whether application of Veregen(r) could induce histological resolution of uVIN when assessed at 32 weeks following the start of treatment. Histological resolution is defined as the absence of uVIN lesion or invasive cancer. The secondary objectives were to assess: clinical resolution (as measured by [?]30% reduction in the sum of the longest diameter of all lesions when compared to baseline), treatment compliance, safety and tolerability, and quality of life using McGill pain questionnaire[8] and Dermatology Life Quality Index (DLQI)[9] questionnaire. The primary endpoint; best histological response observed across the 32 weeks as established by blinded pathology review; was to be analysed as per Jung's design, an analogue of Simon's design, for randomised phase II trials. The trial was designed to have type I and type II error rates less than or equal to 0.15. Assuming that the VIN resolution rate in the control arm would be 10%, and that an improvement to 30% would be clinically important, a required total of 28 patients were to be randomised to each arm. At least 3 more cases of histological resolution at 32 weeks on the experimental arm compared to the control arm of the trial were required in order to conclude sufficient activity.

Clinical resolution was measured according to a protocol defined evaluation criteria based on RECIST, the number of patients with clinical resolution will be reported by treatment arm and proportions will be compared using 2-sample test for equality of proportions with continuity correction. Time to clinical resolution was measured as the time from randomisation to clinical resolution, patients not having resolution were censored at the date last seen, and this will be presented in a Kaplan-Meier plot. Treatment compliance were summarised at patient level taking into account both dose reductions and interruptions. Adverse event data was collected as per Common Terminology Criteria for Adverse Events (CTCAE v4.0), summary tables were presented for this data. Quality of life questionnaire scores were presented using informative plots over

time.

Results

Baseline characteristic of the study cohort

A summary of patient characteristics in the cohort is outlined in Table 1. A total of 26 patients with histological confirmation of uVIN were recruited into our study, and an equal number of patients were randomised into Veregen(r) (n=13) or placebo (n=13) treatment arms. The mean age of our cohort was 51 years old; 25 (96.2%) patients recruited presented with recurrent disease, and only 1 (3.8%) patient had primary uVIN. Our patient cohort has a long-standing history of uVIN with a mean presentation of 10.70 years (1.04, 30.38 years); these patients also suffered from long-term symptoms with a mean duration of 22.78 months prior to randomisation (Table 1). Over half of the patients (53.8%, n=14) presented with a unifocal uVIN lesion, with the remainder (n=12, 46.2%) presenting with multifocal lesions; two patients presented with five separate lesions. The baseline means cumulative lesion size was 3.46cm (1.00, 12.50cm). The majority of our patients were either current cigarette smokers (57.7%, n=15) or ex-smoker (34.6%, n=9); only two patients have never smoked.

The majority of patients (n=25, 80.8%) received either previous medical, surgical or both modalities of treatment, with only three patients receiving no prior treatment before being randomised into accepting Veregen(r). Data for two patients were unavailable. Most of these patients (n=20) had undergone surgical excision, while eight patients were previously treated with Imiquimod. In addition, five patients had also received laser ablative treatment prior to randomisation. A total of nine patients had multimodality treatments, six patients receiving two different treatment modalities, and three patients receiving three different treatment modalities. Only one patient did not have surgery but received ablative therapy and Imiquimod on separate occasions (Table 1).

Topical application of Veregen(r) is relatively well tolerated by patients

Patients were advised to apply the ointment three times daily for 16 weeks. Nineteen patients remained on treatment for 16 weeks, 10 in the placebo arm and 9 in the Veregen(r) arm. Percentage administered, taking into account both reductions and interruptions was determined for each patient, the Veregen(r) arm had mean percentage administered of 69.94% in contrast to the placebo arm with 86.43%.

Overall, there was a higher number of patients who reduced the frequency of ointment application in the Veregen(r) group compared to the placebo group; 52 dose reductions in 11 patients and 70 dose reductions in 12 patients, respectively. Concomitant medications such as Paracetamol, NSAIDs and 1% topical lignocaine ointment were permitted to be used along Veregen(r)/placebo treatment to help alleviate symptoms caused by either the trial medication or uVIN. At baseline, only three patients in Veregen(r) group were using concomitant medication and none in the placebo group. On trial, 2 patients on the placebo arm used paracetamol and Sudocrem, respectively, whilst on the Veregen(r) arm, 7 patients used lignocaine with and one patient also took oral simple analgesia for pain control.

The adverse effects which relate to the use of trial ointments are detailed in Table 2. Baseline uVIN symptoms reported prior to starting trial medications were burning, erythema multiforme, pain and pruritus, with itchiness being the most typical symptoms. In one patient, the severity of erythema multiforme was reported as grade 4. Overall, most adverse events reported were grade 1, 89% in placebo and 74% in Veregen(r) group. Grade 3 and 4 adverse events were only reported in Veregen(r) group and collectively, only two patients suffered from such symptoms. One of the patients who reported a grade 4 adverse event was presented with underlying grade 4 erythema multiforme. The other patient who complained of a grade 3 adverse event had a burning sensation. One patient did not report any adverse events, she was in the placebo group. There was a single serious adverse event, reported in the Veregen(r) group, with upper respiratory symptoms who was subsequently diagnosed as lower respiratory tract infection, an even unrelated to Veregen(r) toxicity. Supplementary Table 1 lists the adverse effects reported with the application of Veregen(r) and placebo. All adverse effects experienced by the patients were fully resolved to baseline upon stopping the medication

Patients randomised into Veregen(r) arm showed a significantly better clinical response when compared to placebo

Clinical response was measured according to a protocol defined evaluation criteria based on RECIST and responses were categorised into stable disease, partial response, complete response and progressive disease. Clinical responses were measured at 4, 8, 16, 32 and 52 weeks after the start of treatment: 5 patients showed partial response in Veregen(r) group when compared to only one patient in the placebo group at four weeks; 7 patients showed clinical response in Veregen(r) group and 3 in the placebo group at eight weeks. At the end of treatment, 16 weeks, 10 patients in Veregen(r) group responded to treatment: 5 showed complete response; 5 a partial response; 2 patients had stable disease; 1 patient was lost to follow up but responded partially at four weeks. In the placebo group, five patients showed clinical response: 2 complete response, 3 partial response, 4 with stable disease and 1 had progressive disease. Two patients were lost to follow up in the placebo group. At 32 weeks, one patient had progressed in Veregen(r) treatment arm, who previously had a partial response. This patient continued to have disease progression at 52 weeks follow up. One other patient in the Veregen(r) treatment arm, who already had a complete response at 16 weeks, recurred at 52 weeks. In the placebo treatment arm, two patients presented with progressive disease, one patient with previously complete response at 16 weeks relapsed, and two further patient with previous complete response and partial response remained disease-free, the remaining patients had stable disease. In the Veregen(r) group, all patients showed a significant clinical response as opposed to only five patients showing clinical response following treatment (p=0.003) (Figure 1). Patients in the Veregen(r) group show a decreased time to clinical resolution as compared to placebo, both when clinical resolution is taken to be complete response and complete/partial response (Figure 1).

Biopsies were obtained at 16 and 32 weeks after treatment to evaluate the histological resolution of uVIN and there was no observed difference in best histological response in these two groups. Three patients in each arm showed complete histology resolution; 7 and 6 patients in placebo and active arm, respectively, had persistent disease histologically; 3 and 4 patients in placebo and active arm, respectively, refused post-treatment biopsy. One patient from the placebo group developed early-stage squamous cell carcinoma at 16-week biopsy, she was withdrawn from the study and managed according to our local guideline for vulvar cancer.

Baseline pain symptoms and quality of life scores related to uVIN were reported to be better following Veregen(r) treatment

McGills pain questionnaire and DLQI questioners were used to assess changes in the symptoms of pain and quality of life (QoL) at each clinical visit. Baseline questionnaires were completed prior to starting treatment, and the scores from the questioners at each clinical visits were compared to baseline. Over 52 weeks, there was no discernible difference in pain symptoms and QoL score when compared to baseline in the placebo group. In the Veregen(r) group, symptoms of pain were reported to be lower than baseline after patients completed 16 weeks of treatment and remained stable at 32 weeks follow up (Figure 2a). In the QoL index, there is a trend towards an improvement in QoL score in Veregen(r) group after 16 weeks treatment and QoL scores, in general, has remained lower than baseline at 32 weeks (Figure 2b).

Discussion

Main findings

Our study demonstrates that Veregen(r), a topical EGCG ointment, is not only safe but potentially effective in the treatment of uVIN. All patients in the Veregen(r) treatment arm showed at least a partial clinical response with only 2 patients showing disease progression and recurrence, respectively, at 52 weeks follow up. Results from DLQI and McGills pain scores suggest a trend towards symptom improvements following Veregen(r) treatment when compare to baseline and placebo, thus, implicating that topical application of EGCG treatment offers symptoms relieve in these patients. Although approximately 30% of patients in the Veregen(r) group did not adhere to treatment protocol and had to reduce treatment dose or prematurely stop treatment, the side effects profiles were reasonably good with the majority of patients experiencing grade 1

or 2 toxicity in the form of localised irritation. When compared to baseline or pre-treatment, many patients already had underlying symptoms of local irritation, and Veregen(r) treatment *per se* did not worsen their symptoms substantially. Moreover, all the adverse effects reported by patients were fully reversible upon stopping Veregen(r) treatment.

Strengths and Limitations

The main strength of our study lies in the fact that our study was randomised double-blind controlled in nature and all histological assessments were reviewed and reported centrally by an accredited pathologist specialising in gynaecological oncology. Due to funding constraints and the rarity of the disease, we were not able to achieve our intended recruitment target in time and in a single centre setting. Furthermore, as a tertiary referral central, which manages complex pre-malignant and malignant vulval disease, our patient cohort comprised mainly of those who have a refractory disease with previous multiple treatment failure. Hence, there was lack of patients with primary uVIN in our cohort. Nevertheless, we were able to demonstrate that Veregen(r) treatment led to clinical improvements both objectively, through a reduction in lesion size and subjectively through patients QoL and symptoms assessment.

Interpretation

Veregen(r) ointment comprises of 10% Epigallocatechin-3-gallate (EGCG), the primary bioactive polyphenol of green tea. EGCG has been shown to possess anti-carcinogenic effects in both cell culture systems *in vitro* and animal models of cancer *in vivo* .[11-13] A meta-analysis by Tzellos *et al* . showed that application of Veregen(r) ointment to genital warts, a hyperproliferative disease caused by persistent infection with low-risk HPV strains (LR-HPV), is effective in eradicating the lesions with a relatively low recurrence rate.[7] In addition, Veregen(r), unlike Imiquimod, is well tolerated by most patients, with minimal localised side effects such as skin irritation, which is reversed after treatment cessation.

Here, we demonstrated that application of Veregen(r) ointment leads to at least partial clinical resolution to uVIN lesion with potential improvements in symptom of pain and quality of life. Scientific study has shown that EGCG down-regulates expression of the high risk-HPV-encoded E6 and E7 proteins, which are required for cell growth transformation and efficient replication during the HPV life cycle.[12] As topical EGCG has been proven to be effective in the clinical treatment of HPV induced hyperproliferative disorders, coupled with the fact that several *in vitro* studies have shown a marked reduction in proliferation of HR-HPV driven cancerous cell lines[11], presumably through downregulation of the viral oncogenes[12,13], more prolonged-term treatment or maintenance therapy with Veregen(r) could potentially result in complete histological resolution of uVIN. With clinical evidence showing that patients with genital warts who achieved full disease resolution following Veregen(r) treatment were less likely to experience disease recurrence, we speculate that this effect may extend to uVIN[7,14].

As the risk of progression from uVIN to vulval cancer is relatively low,[5] and symptom control is often the primary treatment aim for these women, we propose that Veregen(r) may potentially be an alternative long-term treatment to surgery or act as an adjuvant treatment for surgery, given that surgical treatment does not offer a cure as optimal surgical resection margin was not often achieved, and most patients will recur within three years even if the disease was completely resected, and further surgery is associated with psychosexual comorbidities[10]. Furthermore, Veregen(r) treatment may reduce the frequency or even delay the need for surgical intervention.

Nevertheless, there was no observed difference in best histological response between Veregen(r) and the placebo group and this could be attributed to a number of reasons. Firstly, our study did not achieve the intended recruitment target within the allotted time, and we were unable to extend our recruitment time due to cost and time constrain. Secondly, as a tertiary referral centre, all the patients, except one, who were recruited into our study had a refractory disease as these patients had long-standing symptoms and had experienced multiple treatment failures in the past. Thus, patients with primary disease may show a better histological response to Veregen(r) treatment. Thirdly, extended treatment duration may be required to induce histological resolution of the disease. In two previous independent randomised control studies that

evaluated the use of Imiquimod vs placebo[15] and Imiquimod vs Cidofovir (RT3VIN study),[16] respectively, these studies examined patients with VIN grade 1, 2 and 3. In the former study, there was a significant reduction in disease severity/grade following Imiquimod treatment, an observation which we were not able to undertake in our study as histological assessment in our study were based on The International Society for the Study of Vulval Disease which uses morphological criteria to classify vulval intraepithelial neoplasia into usual-type (HPV-related) or differentiated (non-HPV-related).[17] Thus, women with low grade squamous intraepithelial neoplasia (LSIL) and VIN2 were excluded from our study; hence, the lack of observed difference in histological resolution, despite clinical symptoms and lesion size improvements, maybe because our patient had a higher-grade disease. Moreover, the RT3VIN study found that less than half of the patients treated with either Imiquimod or Cidofovir showed a complete histological response, thus highlighting that longer treatment duration or maintenance treatment may be required to facilitate histological resolution. Future study should consider including patients with LSIL and VIN2 as these patients also suffer from similar debilitating symptoms to that of VIN3 and surgery may be avoided in this group of patients.

Conclusion

Our study demonstrated that Veregen(r) is not only safe but results in at least a partial clinical resolution of uVIN lesions in all patients. Furthermore, we show that Veregen(r) treatment also offers symptoms improvement and a potentially better quality of life. Together, our result suggests that further phase 3 randomised controlled study is warranted to evaluate the efficacy of Veregen(r) in a sizeable multicentre setting to include patients with primary and recurrence disease. Lastly, as Veregen(r) ointment is relatively well tolerated with minimal side effects, there is a possibility for increasing treatment duration beyond currently recommended 16 weeks, as prolonged treatment may lead to a histological resolution of uVIN.

Disclosure of Interest

This study was part funded by Medigene AG, Germany, who supplied Veregen(r) and placebo ointment. Medigene AG did not participate in designing and conducting the clinical trial or recruiting patients into the study. Neither did Medigene AG has any input in reporting the study outcome nor writing the manuscript. None of the authors hold any role in Medigene AG.

Author Contributions

JY, CD and DL conceived the idea for the study, participated in its design and coordination, and provided final approval of the version to be published. JY, DL and SB recruited patients into the study. RG reviewed histological diagnosis. HG, AH and BK undertook data management. DS performed statistical analysis. JY, CD, DS and DL wrote the manuscript and all authors read and approved the final manuscript.

Ethics approval and consent to participate

This study is approved by the East Midlands - Derby Research Ethics Committee on 20th December 2013 with study number 13/EM/0398. All patients provided a written consent to participate in the study. Clinical trial registration details: EudraCT number: 2013-003107-19; ISRCTN number: 98495886; Trail open date: 01/01/2014; first recruitment date: 13/10/2014; URL: http://www.isrctn.com/ISRCTN98495886

Funding

The study is jointly funded by the National Institute for Health Research via the Research for Patient Benefit programme and Medigene AG, Germany, supplied Veregen(r) and placebo.

Acknowledgements

We like to thank the clinical research department of Sandwell and West Birmingham Hospital NHS Trusts and Dr Brian Gammon for their efforts in coordinating this clinical study.

Supporting information

Table 1. Patients' characteristics

Table 2. Grade of adverse events reported by patients with Veregen(r) and placebo treatment

Figure 1. Kaplan-Meir plot showing time to clinical resolution of uVIN lesions in Veregen(r) and placebo.

Figure 2a. McGill Pain score reported by patients over time at baseline and after starting Veregen(r) and placebo treatment.

Figure 2b: Dermatology Quality of Life (QLDI) score reported by patients over time at baseline and after starting Veregen(r) and placebo treatment.

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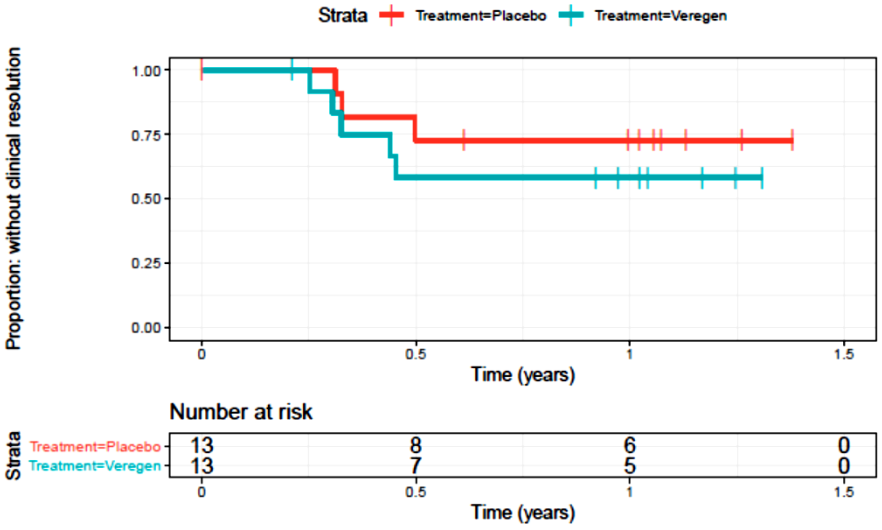

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Variable	Level	Overall N (%)	Placebo N (%)	Veregen N (%)
First VIN episode	No	25 (96.2)	12 (92.3)	13 (100)
	Yes	1 (3.8)	1 (7.7)	0 (0)
Prior Treatment: Imiquimod	No	18 (69.2)	8 (61.5)	10 (76.9)
	Yes	8 (30.8)	5 (38.5)	3 (23.1)
Prior Treatment: Laser/Diathermy ablation	No	21 (80.8)	10 (76.9)	11 (84.6)
	Yes	5 (19.2)	3 (23.1)	2 (15.4)
Prior Treatment: Other Topical Cream	No	26 (100)	13 (100)	13 (100)
Prior Treatment: Other Treatment	No	26 (100)	13 (100)	13 (100)
Prior Treatment: Surgery	No	6 (23.1)	2 (15.4)	4 (30.8)
	Yes	20 (76.9)	11 (84.6)	9 (69.2)
Smoking Status	Current	15 (57.7)	9 (69.2)	6 (46.2)
	Never	2 (7.7)	1 (7.7)	1 (7.7)
	Previous	9 (34.6)	3 (23.1)	6 (46.2)
Variable	Summary	Overall	Placebo	Veregen
Time: first clinical diagnosis to rand (years)	Mean (sd)	10.70 (8.2)	12.66 (10.1)	8.90 (6.0)
	Missing	3	2	1
	N	23	11	12
	Range	1.04, 30.38	1.04, 30.38	1.28, 25.41
Time: first histological diagnosis to rand (years)	Mean (sd)	10.33 (8.5)	12.85 (10.5)	8.50 (6.7)
	Missing	7	5	2
	N	19	8	11
	Range	0.06, 30.38	1.04, 30.38	0.06, 25.41
Time: first symptom to rand (years)	Mean (sd)	12.20 (8.3)	14.43 (10.2)	10.19 (5.9)
	Missing	7	4	3
	N	19	9	10
	Range	3.01, 30.38	3.26, 30.38	3.01, 25.41
Time: start of current VIN to rand (Months)	Mean (sd)	22.78 (33.3)	30.22 (44.0)	15.33 (16.0)
	N	26	13	13
	Range	0.47, 148.97	0.70, 148.97	0.47, 45.87
Age (years)	Mean (sd)	51.01 (12.5)	49.40 (13.2)	52.62 (12.0)
	N	26	13	13
	Range	23.73, 72.96	23.73, 67.93	28.30, 72.96

Grade	Overall Events (Patients)	Placebo Events (Patients)	Veregen Events (Patients)
1	159 (24)	75 (12)	84 (12)
2	32 (14)	9 (5)	23 (9)
3	1 (1)	0 (0)	1 (1)
4	1 (1)	0 (0)	1 (1)
	4 (2)	0 (0)	4 (2)