Acta Derm Venereol (Stockh) 1993; 73: 385–387

Interferon Alpha-2b Treatment of Symptomatic Chronic Vulvodynia Associated with Koilocytosis

JOHN LARSEN[1], KURT PETERS[3], CARSTEN SAND PETERSEN[1], KIRSTEN DAMKJÆR[4], JENS ALBRECTSEN[2] and KAARE WEISMANN[3]

Departments of [1]Dermatology and [2]Pathology, Rigshospitalet and Departments of [3]Dermatology and [4]Pathology, Bispebjerg Hospital, University Hospitals of Copenhagen, Denmark

In an open study with identical criteria for diagnosis, 16 female patients with typical symptoms of chronic vulvodynia associated with acetowhitening of the vestibular epithelium and koilocytosis in biopsy specimens received recombinant interferon alpha-2b 5 MIU intralesionally 3 times weekly for 3 weeks or subcutaneously 3 times weekly for 8 weeks. Three months after end of therapy, clinical symptoms had disappeared in 7 (70%) of the 10 patients treated intralesionally, compared with only one (16%) of the 6 patients treated subcutaneously. In addition, the last 3 (30%) patients in the first group had a partial response to therapy. The acetowhitening persisted in all patients. The koilocytosis remained unchanged in 13 (81%) of the 16 patients. Our results indicate that recombinant interferon alpha-2b administered intralesionally seems to be efficacious in reducing clinical symptoms in vulvodynia with suspected human papillomavirus infection but does not eliminate the infection. Subcutaneous administration had neither symptomatic nor antiviral effect. A placebo-controlled study is needed, but with our present knowledge we recommend intralesionally administered interferon as a symptomatic treatment of vulvodynia. ***Key words: Vulvitis; Human papillomavirus.***

(Accepted April 5, 1993.)

Acta Derm Venereol (Stockh) 1993; 73: 385–387.

J. Larsen, Department of Dermato-venereology, Rigshospitalet, University Hospital of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark.

Vulvodynia is characterized by vulvar discomfort, especially the sense of burning. One subset of vulvodynia is vestibulitis, and infection with human papillomavirus (HPV) may be associated in some cases (1). Diagnosis is often stated late in the course of the disease and treatment is a major problem. Surgical procedures in the form of CO_2-laser treatment (2–5) and vestibulectomy with vaginal advancement (2,3,5–9) have been performed with some success. Especially vestibulectomy has shown good results but is quite mutilating. Treatment with interferon may be a more acceptable therapy for the patient. This treatment modality has been tried with subcutaneously/intramuscularly (sc/im) (10) as well as intralesionally (il) (11–13) administered doses. We have treated a group of females, all with symptomatic chronic vulvodynia, acetowhitening of the vestibular epithelium and koilocytosis, with either sc or il administered recombinant interferon alpha-2b (rIF-α-2b) (Intron-A, Schering-Plough). Our data indicate that il administered rIF-α-2b, in contrast to sc administered rIF-α-2b, alleviates vulvodynia; it does not, however, affect the acetowhitening or the koilocytosis.

PATIENTS AND METHODS

The study took place from June 1989 to October 1992 in two departments. Only two doctors were involved in the treatment and control of the patients. Patients included were non-pregnant women, older than 18 years, presenting with typical symptoms of vulvodynia for at least 6 months associated with acetowhitening of the vestibular epithelium and koilocytosis in biopsy specimens taken before treatment. All patients had frequent experiences of vulvar burning, external dyspareunia and a tendency of fissuring at the posterior commissure. The symptoms could present spontaneously as well as following mechanical provocation, e.g. coitus, gynecological examination, use of tampons, bicycling or use of tight clothing.

Application for 3 min of acetic acid 3% on the mucosal epithelium of the minor labiae showed acetowhitening in all cases. The acetic acid test and biopsies for histopathologic examination were performed before treatment, immediately after, 1 month and 3 months after treatment.

Treatment response was characterized according to the patient's subjective judgement as complete response (CR) (total disappearance of vulvodynia), partial response (PR) (reduction of vulvodynia) or no response (NR) (vulvodynia unchanged) 1 and 3 months after conclusion of the treatment. The patients registered side-effects during and after treatment.

The patients were treated in two groups with interferon, differing in the method of administration and in total dose. Six patients were treated with rIF-α-2b 5 MIU sc 3 times weekly for 8 weeks. Interferon was diluted in 1.0 ml of isotonic saline and injected in the thigh. Ten patients were treated with rIF-α-2b 5 MIU il 3 times weekly for 3 weeks. The intralesional injections were performed as shown in Fig. 1.

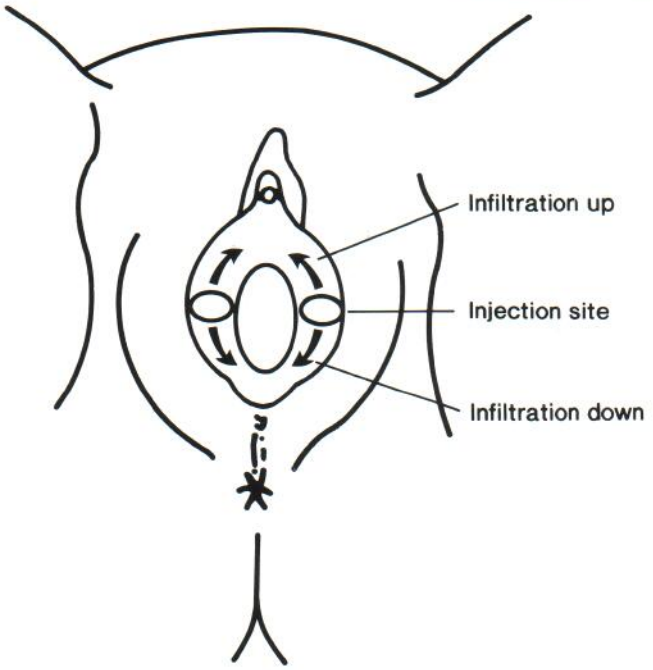

Fig. 1. Localization of intralesional injection with interferon alpha-2b.

Table I. *Effect of treatment with interferon alpha-2b (rIF-α-2b) administered subcutaneously (sc) and intralesionally (il) 3 months after therapy*

CR = complete response. Total disappearance of vulvodynia.
PR = partial response. Reduction of vulvodynia.
NR = no response. Vulvodynia unchanged.

rIF-α-2b	Symptoms			Disappearance of koilocytosis
	CR	PR	NR	
sc	1 (16%)	0 (0%)	5 (74%)	1/6 (16%)
il	7 (70%)	3 (30%)	0 (0%)	2/10 (20%)

The 5 MIU of interferon were diluted in 0.6 ml of isotonic saline. Centrally in each minor labium 0.3 ml of the solution was injected and distributed upwards and downwards, 0.15 ml in each direction, using a 1.0 ml syringe and a 27 gauge needle. In order to reduce local pain EMLA cream was applied 6–7 min prior to the injection. To diminish the side-effects, all patients received 1 g of acetaminophen at the time of injection and, if needed, additional 1 g twice to 3 times on the day of treatment.

Blood tests were done before and weekly during the treatment. These were haematology (red blood cell count, white blood cell count with differential, platelet count) and clinical chemistry (alkaline phosphatase, alanine aminotransferase, total bilirubin). Before treatment all the patients had negative or normal tests for cervical cell atypia (SMEAR), pregnancy, venereal diseases (chlamydia, gonorrhoea, *Trichomonas vaginalis* and *Gardnerella vaginalis*, *Candida albicans*). All patients were HIV-antibody negative. Using Student's *t*-test the two groups receiving different treatments were statistically comparable ($p < 0.05$) as to age and period of symptoms (Table II).

RESULTS

The response to treatment and the results of the histologic examinations are shown in Table I. Only one (16%) of the 6 patients treated with rIF-α-2b sc had symptomatic relief, while the rest had no response. In 7 (70%) of the 10 patients treated with rIF-α-2b il symptoms disappeared 1 to 3 months after stopping therapy. In addition, a reduction in severity of the symptoms was obtained in the remaining 3 patients treated il. The acetowhitening persisted in all patients. The koilocytosis was unchanged in 13 (81%) of the 16 patients treated.

All patients experienced typical flew-like side-effects, especially after the initial injections. The symptoms declined in most of the patients during the treatment course. None of the patients stopped therapy due to side-effects or due to no effect of the treatment. None of the patients developed leukopenia, thrombocytopenia or signs of hepatotoxicity.

Table II. *Patient's age and the duration of symptoms at the time of treatment with interferon alpha-2b (rIF-α-2b) subcutaneously and intralesionally*

Regimen	Mean and (range) in years	
	Age	Duration of symptoms
Subcutaneous (sc)	28.5 (22–52)	3.75 (2–5)
Intralesional (il)	30.2 (19–39)	3.10 (0.5–7)

DISCUSSION

Vulvodynia is "chronic vulvar discomfort, especially that characterized by the patient's complaint of burning, stinging, irritation, or rawness" (14). The aetiology is multifactorial and treatment often has to be directed against different factors depending on the symptoms of the individual patient (15). At the moment vulvodynia is divided into six subsets. One of these is vulvar vestibulitis, which may be associated with HPV infection (16). Vulvodynia constitutes a therapeutic problem and several treatment modalities have been tried, e.g. locally with podofyllin, podofyllotoxin, 5-fluorouracil and surgical measures as CO_2-laser and vestibulectomy with vaginal advancement. Vestibulectomy has proved to have a high cure rate (3,5–8) but is rather mutilating and must be regarded as the final attempt after failure of other methods. Interferon may have an effect on diseases in which the pathophysiology is assumed to involve viral and immunological factors, and a beneficial effect of im administered interferonbeta in HPV-associated vestibulitis has been reported (10). rIF-α-2b has proven to have some effect in treating genital warts (17–19). The sc method of administrating the interferon is obviously much less uncomfortable to the patient. Based on this we decided to use this method in the first 6 patients diagnosed in the departments. If the results were unsatisfactory – and this was the fact – the next patients should be treated il. In both groups we used higher doses compared to most previous reports to prevent that too small doses would result in treatment failure. The sc treatment was given for 8 weeks while the il was given for 3 weeks based on the assumption that the effect of interferon may be increased when injected locally.

Our results indicate that il administration of rIF-α-2b induces a symptomatic beneficial effect in some women with chronic vulvodynia, whereas sc administrated rIF-α-2b has no effect. Our patients have been followed for 12 to 24 months after treatment, and we cannot exclude the possibility that symptoms may recur.

We established the diagnosis based on the presence of typical symptoms (vulvar burning, external dyspareunia and fissuring) combined with the patients' history (frequent negative microbiological tests and non-effective treatments), acetowhitening of the epithelium and histology (koilocytosis).

Previously HPV DNA has been found in 24 of 50 women with vulvodynia and subclinical HPV infection (koilocytosis in biopsy specimens) using a Southern-blot assay (20). Neither il nor sc administration of rIF-α-2b had antiviral activity, which indicates that the aetiology of vulvodynia is multifactorial. A placebo-controlled study will be needed to substantiate our findings and to exclude the possibility that the mere injection of an indifferent solution or the intensive care of the patient may reduce the vulvar symptoms. In view of the data presented we recommend il rIF-α-2b as a symptomatic treatment in women with vulvodynia.

REFERENCES

1. Vulvar vestibulitis and vestibular papillomatosis: report of the ISSVD Committee on Vulvodynia. J Reprod Med 1991; 36: 413–415.

2. Reid R, Greenberg MD, Daoud Y, Husain M, Selvaggi S, Wilkinson E. Colposcopic findings in women with vulvar pain syndromes – a preliminary report. J Reprod Med 1988; 33: 523–532.
3. Michlewitz H, Kennison RD, Turksoy RN, Fertitta LC. Vulvar vestibulitis – subgroup with Bartholin gland duct inflammation. Obstet Gynecol 1989; 73: 410–413.
4. Shafi MI, Finn C, Luesley DM, Jordan JA, Rollason TP. Carbon dioxide lasertreatment for vulval papillomatosis (vulvodynia). Br J Obstet Gynecol 1990; 97: 1148–1150.
5. Marinoff SC, Turner MLC. Vulvar vestibulitis syndrome: an overview. Am J Obstet Gynecol 1991; 165: 1228–1233.
6. Woodruff JD, Parmley TH. Infection of the minor vestibular gland. Obstet Gynecol 1983; 62: 609–612.
7. Peckham BM, Maki DG, Patterson JJ, Hafez G-R. Focal vulvitis: a characteristic syndrome and cause of dyspareunia. Am J Obstet Gynecol 1986; 154: 855–864.
8. Marinoff SC. Vestibulitis and essential vulvodynia. ISSVD Tutorial Reporter, March 1991: 7.
9. Weström L. Vulvar vestibulitis. Lancet 1991; 338: 1088.
10. Bornstein J. HPV-associated vulvar vestibulitis: treatment by intramuscular interferon-beta. J Interferon Res 1991; vol. 11, symp. 1.
11. Hatch KD. Interferon alpha-2 (Intron-A) for human papillomavirus vaginitis and vulvitis. J Reprod Med 1988; 33: 718.
12. Horowitz BJ. Interferon therapy for condylomatous vulvitis. Obstet Gynecol 1989; 73: 446–448.
13. Kent HL, Wiesniewski PM. Interferon for vulvar vestibulitis. J Reprod Med 1990; 35: 1138–1140.
14. Burning vulva syndrome: report of the ISSVD Task Force. J Reprod Med 1984; 29: 457.
15. McKay M. Subsets of vulvodynia. J Reprod Med 1988; 33: 695–698.
16. Turner MLC, Marinoff SC. Association of human papillomavirus with vulvodynia and the vulvar vestibulitis syndrome. J Reprod Med 1988; 33: 533–537.
17. Vance JC, Bart BJ, Hansen RC, et al. Intralesional recombinant alpha 2b interferon for the treatment of patients with condyloma acuminata or verruca plantaris. Arch Dermatol 1986; 122: 272–277.
18. Eron JL, Judson F, Tucker S, et al. Interferon therapy for condyloma acuminata. N Engl J Med 1986; 315: 1059–1064.
19. Reichman RC, Oakes D, Bonnez W, et al. Treatment of condyloma acuminatum with three different interferons administered intralesionally. Ann Intern Med 1988; 108: 675–679.
20. Bodén E, Rylander E, Evander M, Wadell G, von Schoultz B. Papilloma virus infection of the vulva. Acta Obstet Gynecol Scand 1989; 68: 179–184.