

A Pilot Study of the Efficacy and Tolerability of Intralesional Recombinant Human Beta-Interferons in Cervical Intraepithelial Neoplasia

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Abstract

Beta-interferons possess anti-viral, cell proliferation inhibition and immunomodulatory characteristics which may be of use in the treatment of cervical intraepithelial neoplasia (CIN). Intralesional administration may avoid systemic side effects. Twenty-six women with cervical punch biopsy proven CIN I and II were treated by interferon injection into the cervical transformation zone according to three dosage regimens—6 million international units (IU) weekly for six weeks, 9 million IU weekly for six weeks and 12 million IU bi-weekly for three weeks. At the last treatment visit, cervical cytology and biopsy were taken to ensure no disease progression and large loop excision of the transformation zone (LLETZ) was carried out six months after treatment.

Therapy was well-tolerated with 93% of the scheduled 156 treatments given. Side effects which caused cessation of treatment included severe myalgia, headaches and prolonged flu-like symptoms. The 2 patients who failed to attend for LLETZ at six months and another 2 patients who received fewer than five scheduled treatments were excluded from analysis. LLETZ histology was negative in 12 patients (54%), showed inflammatory changes or squamous metaplasia in 4 (18%), was unchanged in 4 patients and had progressed in 2 (10%).

Whilst intralesional beta-interferon clearly has activity in CIN, the response rate is less than that seen for excisional or ablative procedures. Nevertheless, it may have a role in the management of CIN where, for medical reasons of patient preference, there is a desire to avoid surgical therapy.

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Introduction

Cervical intraepithelial neoplasia (CIN) is a neoplastic disorder in which infection with sub-types of the human papillomavirus appears to play an important aetiological role.¹ The interferons are a family of proteins which possess anti-viral action, inhibit cell proliferation and modulate the natural immune response² and which therefore may be active in the treatment of CIN. Over the past decade, the therapeutic actions of several different natural interferons administered via a variety of routes have been studied in women with CIN.³ In general, beta-interferons have greater activity than alpha-interferons and intralesional injection is the preferred route of administration, being effective whilst avoiding the frequent severe side-effects associated with systemic therapy.⁴ The potential advantages of effective medical therapy of CIN over surgical treatment are that no special expertise or equipment is required and that the cervix is not physically damaged, thus avoiding the

long-term complications of cervical incompetence or stenosis.

The recombinant human beta-interferon (RHBI) used in this study was produced from cultured Chinese hamster ovary cells into which the human gene for beta-interferon has been inserted using recombinant DNA methodology and in terms of molecular weight, amino acid sequence, molecular structure and biological activity is virtually identical to natural human beta-interferon.

The aims of this phase I/II study were firstly to determine whether RHBI has activity in the treatment of CIN and secondly to determine the tolerability of locally administered RHBI.

Subjects and Methods

Twenty-six women who had been referred to the Dysplasia Clinic with abnormal cervical cytology were recruited into the study. All had either CIN I or CIN II on

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colposcopically directed punch biopsy at their initial visit, had a negative pregnancy test and were prepared to use effective contraception for the duration of the study.

Treatment was commenced within 28 days of the initial colposcopy and biopsy. Colposcopy was performed at each treatment visit. At the first and last treatment visits the percentage of the transformation zone which was colposcopically abnormal was recorded. RHBI was supplied as a lyophilised powder in vials stored at 2°C to 8°C. Each vial contained 6 million international units (IU) of RHBI which was reconstituted with 1 ml of sterile water for injection immediately prior to use. One quarter of the total dose was injected into each quadrant of the transformation zone at each visit, according to the following dosage regimen:

6 million IU weekly for 6 weeks	5 patients
9 million IU weekly for 6 weeks	10 patients
12 million IU bi-weekly for 3 weeks	11 patients

At the last treatment visit a smear and colposcopically directed punch biopsy were taken to ensure that there had been no disease progression during the course of the therapy. Subjects were asked to record the nature, time of onset and duration of any adverse symptoms experienced during treatment.

Finally, a smear and large loop excision of the transformation zone (LLETZ) were performed 6 months after the start of treatment.⁵

TABLE I: PRETREATMENT CYTOLOGY AND HISTOLOGY

Cytology	
Negative	1
Inflammatory	2
Mild dyskaryosis	14
Moderate dyskaryosis	9
Histology	
CIN I	16
CIN II	10

TABLE II: OCCURRENCE OF MYALGIA

Dose	6 million IU weekly (n = 23 treatments)	9 million IU weekly (n = 59 treatments)	12 million IU bi-weekly (n = 63 treatments)
Side effects			
None (chi-square <0.01)	9 (39%)	14 (24%)	2 (3%)
Moderate/severe myalgia (chi-square <0.01)	1 (4%)	3 (5%)	20 (32%)
Myalgia lasting >48 hours	0	2 (3%)	18 (29%)

The study was approved by the Research Ethics Committee of King’s College Hospital and all subjects gave informed written consent.

Results

The mean age of the 26 women was 27 years (range 19 to 43 years) and all were nulliparous. Twenty-two had no previous history of CIN, but 3 had a past history of apparently successfully treated CIN III (1 cone biopsy, 1 cold coagulation, 1 LLETZ) and 1 a past history of CIN of undefined severity, successfully treated by laser ablation. The results of cervical cytology and colposcopically directed punch biopsy performed at the initial visit prior to RHBI treatment are presented in Table I.

Overall, treatment with RHBI was well tolerated. Out of 156 scheduled treatments, 145 (93%) were actually given. In the 6 million IU weekly group, 1 subject abandoned the study after the first treatment because of severe myalgia and 2 subjects withdrew after the fifth treatment, 1 because of progressively severe headaches after each successive treatment and 1 because of prolonged myalgia of 20 hours duration following the fifth treatment. In the 9 million IU weekly group, 1 subject withdrew because of prolonged “flu-like” symptoms lasting 5 days after the fifth treatment. In the 12 million IU bi-weekly group, 2 subjects were withdrawn from the study, 1 (an intravenous drug user) after the fourth treatment because of persistent upper limb petechiae (platelet count normal) and the other after the fifth treatment because of pregnancy (which was subsequently terminated).

The most common side-effect reported was “flu-like” symptoms of generalised myalgia, which increased in frequency and severity with escalation of the dose of RHBI, as presented in Table II. Transient vaginal bleeding was reported following 3 treatments.

TABLE III: CHANGE IN HISTOLOGY OF CERVICAL TRANSFORMATION ZONE 6 MONTHS AFTER TREATMENT WITH RECOMBINANT HUMAN BETA-INTERFERON

6 million IU weekly (n = 4)		9 million IU weekly (n = 9)		12 million IU bi-weekly (n = 9)	
Initial	6 months	Initial	6 months	Initial	6 months
CIN I	inf	CIN I	neg	CIN I	neg
CIN II	inf	CIN I	neg	CIN I	neg
CIN II	inf	CIN I	neg	CIN I	neg
CIN II	neg	CIN I	CIN I	CIN I	neg
		CIN II	neg	CIN I	neg
		CIN II	neg	CIN I	CIN I
		CIN II	sq met	CIN I	CIN I
		CIN II	CIN III	CIN I	CIN I
		CIN II	CIN III	CIN II	neg

CIN: cervical intraepithelial neoplasia; inf: inflammatory; neg: negative; sq met: squamous metaplasia

Two subjects failed to attend for LLETZ at 6 months and the 2 subjects who received fewer than 5 scheduled treatments were excluded from analysis, leaving 22 subjects with histology from LLETZ at 6 months to compare with histology from the initial pre-treatment colposcopically directed punch biopsy. The change in histology for the individual subjects is presented in Table III. Histology improved in 4/4 (100%) subjects receiving 6 million IU RHBI weekly, in 6/9 (67%) receiving 9 million IU weekly and in 6/9 (67%) receiving 12 million IU bi-weekly. Overall, histology improved with complete regression of CIN in 16 (73%) subjects, remained unchanged in 4 (18%) and progressed to a more severe type of CIN in 2 (9%).

The median (interquartile range) percentage of the transformation zone observed to be colposcopically abnormal was 25% (10% to 30%) before treatment and 0% (0% to 10%) at the end of treatment ($P < 0.001$ Mann-Whitney U test).

Discussion

The results of this uncontrolled pilot study suggest that intralesional injection of recombinant human beta-interferon has activity in the treatment of CIN. The complete response rate of 73% observed in this study is similar to that of 69% seen with natural human beta-interferons⁴ and significantly more than previously noted for spontaneous resolution.

No serious side effects were noted during the course of 145 individual treatment episodes. "Flu-like" symptoms of generalised myalgia occurred frequently and were usually mild, except in the highest dosage group in which severe or prolonged symptoms were associated with one third of treatment episodes. Use of this higher dose did not appear to confer any benefit in terms of therapeutic effect upon CIN. Similar dose-dependent side-effects have previously been reported with RHBI used in other clinical circumstances.^{3,6}

The most obvious disadvantage of RHBI in the treatment of CIN is that it is less effective than surgical excision or ablation of the transformation zone. LLETZ, for example, can be expected to have a treatment failure rate of less than 5%.⁵ A further disadvantage of the treatment regimens employed in this study is that com-

plete treatment required 6 visits to the Clinic. This is both expensive in terms of clinic and physician time, but also presents a compliance problem with the risk that a significant number of women may not be adequately treated. For example, in our inner city practice, approximately 25% of patients fail to attend appointments (Smith and Lawton, unpublished data). For these reasons, RHBI cannot be recommended for the routine treatment of CIN, for which surgical treatment with LLETZ must be recommended. Nevertheless, it may have a role in the treatment of CIN I and CIN II where, for medical reasons or patient preference, there exists a strong desire to avoid surgical therapy. The aim of future research should initially be to prove the efficacy of intralesional recombinant human beta-interferon in a placebo controlled trial and the data from this study indicate that further research should use either the 6 or 9 million IU dose.

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