Effect of perilesional injection of α-interferon on cervical intraepithelial neoplasia and associated human papillomavirus infection

A M Dunham FRCS MRCOG **J C McCartney** MD FRCPath **D J McCance** BSc PhD
R W Taylor MD FRCOG *St Thomas' Hospital, London and Guy's Hospital, London*

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Summary

In this controlled prospective study, 14 patients with cervical intraepithelial neoplasia (CIN) were observed for one month to exclude spontaneous regression, and then seven patients were treated twice-weekly with perilesional injections of α-interferon. Both groups were monitored colposcopically, and advised to use the contraceptive sheath. Cervical smears and biopsies for histology and viral studies were taken before and after the study.

There was an improvement of six out of seven of the study group, with two complete cures. Koilocytosis disappeared if it had been present initially, as did human papillomavirus (HPV) 16. By contrast, three control cases showed improvement, but there were no cures, and one case deteriorated; Koilocytosis (2 cases) did not change; HPV 16 disappeared in two controls and appeared in one.

A new focus of dysplasia appeared in a part of the transformation zone not being treated with α-interferon in one of the study cases, illustrating the advisability of treating the whole transformation zone in CIN.

Introduction

Treatment of CIN is performed by destructive methods (laser, cold coagulation, cryocautery) or excision (by cone biopsy or loop diathermy). In some circumstances, such as recurrence of CIN in the vaginal stump after hysterectomy, such methods may be hazardous or incomplete. It was therefore decided to investigate the use of α-interferon injections around areas of CIN to see whether these would cure the lesions, either by antiviral or antineoplastic action of α-interferon, or both.

One study[1] from Hong Kong used perilesional injections of α-interferon to treat CIN, and produced remission in six out of seven patients. However, in this trial CIN was not confirmed independently by biopsy before treatment, and there were no controls. In the present trial pre-treatment biopsies were taken to confirm CIN, but were followed by a waiting period of a month to exclude spontaneous cure due to trauma[2]. Controls were also included.

Finally, biopsies for identification of HPV 6+16,[3,4] were taken to see if there was any correlation between these viruses, CIN, and α-interferon treatment.

Subjects and methods

Fourteen patients who had been referred to the colposcopy clinic with abnormal smears and had a colpobiopsy confirming CIN were recruited into the trial. Smears had already been taken, and in addition a biopsy of the abnormal area for HPV 6+16 hybridization were obtained. Full blood count and liver function tests were performed before the trial and after α-interferon treatment in the trial group.

After a month's waiting period, a colposcopic assessment excluded spontaneous regression, and the patients were assigned to the study or control groups.

The study patients were colposcoped twice weekly, and 1.5 Mu of α-interferon (Intron A) was injected through a 22 gauge needle at three or four sites peripheral to the lesion at a depth of 0.5 cm. The control group were observed colposcopically for 8 weeks.

After 8 weeks the groups had a complete review: repeat smear and colpobiopsies for histology and virology were taken.

In cases where complete cure had not been achieved over the study period of 12 weeks, laser ablation was performed. In this way the trial patients experienced no delay in the hospital's routine treatment for CIN by laser after a maximum 12 weeks' waiting list.

Histological and cytological reassessment was made by an independent histologist who had no knowledge of which subjects were in the treatment and non-treatment groups.

Biopsies for HPV hybridization were immediately frozen in liquid nitrogen and thawed in batches for DNA analysis for HPV types 6+16.

Results

Six out of seven patients in the α-interferon treatment group showed improvement of histology over the treatment period (Table 1), whereas only three of the control group showed improvement, and one showed deterioration (Table 2). Six out of seven of the α-interferon group showed cytological improvement, whereas only two of the control group showed improvement, and one had deteriorated.

There were two 'cures' in the α-interferon group (complete histological and cytological recovery). There also was a disappearance of koilocytosis histologically and cytologically in all 4 α-interferon-treated patients who showed koilocytosis before treatment.

No HPV type 6 was isolated from the patients. HPV 16 was isolated in three patients from the study group and two controls and later appeared in a third control patient. It disappeared after treatment in the three patients on the α-interferon group, but also spontaneously from two controls. Its presence was not isolated with a more severe lesion, and it was associated with an average response to interferon (one cure and two 'improved', see Table 1).

Colposcopic changes during treatment were of hyperaemia of the cervix lasting 2 weeks and initial

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Table 1. Study group - results

Case	Test	Before IFN	After IFN	Comment	Before IFN HPV	After IFN HPV
1	Histology	CIN 1-2	No CIN	Cured	+16	–
	Cytology	Smear 3A	Smear negative			
2	Histology	CIN 2+Koilo	No CIN	Cured	–	–
	Cytology	Smear 3B	Smear negative			
3	Histology	CIN 2	CIN 1	Improved	+16	–
	Cytology	Smear 3A	Smear negative	(smear normal)		
4	Histology	CIN 2+Koilo	CIN 1-2	Improved	+16	–
	Cytology	Smear 3A+Koilo	Smear 3a			
5	Histology	CIN 3+Koilo	CIN 1-2	Improved	–	–
	Cytology	Smear 3A	Smear negative			
6	Histology	CIN 1	CIN 1 'at most'	Improved	–	–
	Cytology	Smear 3A	Smear negative	(smear normal)		
7	Histology	CIN 2+Koilo	CIN 2	Unchanged	–	–
	Cytology	Smear 3B	Smear 3B	? improved		

Table 2. Control group - results

Case	Test	First assessment	After 8 weeks' study period	Comment	Before no RX HPV	After no RX HPV
8	Histology	CIN 1+Koilo	Koilocytosis no CIN	Improved	+16	–
	Cytology	Smear 3A	Smear 3A	(smear unchanged)		
9	Histology	CIN 1-2	CIN 1	Improved	–	–
	Cytology	Smear 3A+Koilo	Smear 3A+Koilocytosis	(smear unchanged)		
10	Histology	CIN 2	CIN 1	Improved	–	–
	Cytology	Smear 3B	Smear 3A			
11	Histology	CIN 2	CIN 2	Unchanged	–	+16
	Cytology	Smear 3A	Smear 3A			
12	Histology	CIN 3	CIN 3	Unchanged	+16	–
	Cytology	Smear 4	Smear 3B	(smear improved)		
13	Histology	CIN 3	CIN 3	Unchanged	–	–
	Cytology	Smear 3A	Smear 3B	(smear deteriorated)		
14	Histology	CIN 1	CIN 1-2	Deteriorated	–	–
	Cytology	Smear 3A	Smear 3A	(smear unchanged) Histology worsened to CIN 3 four months after laser		

gradual paling of acetowhite and contraction of the lesion. There was an initial dramatic regression of a cervical wart, which later partially recurred. Unexpectedly, a new focus of dysplasia developed in an area of transformation zone not being treated by α-interferon in one patient, whereas the treated area regressed completely.

Discussion

The results of this study support the findings of Choo *et al.*[1] that α-interferon injections cause improvement or cure in CIN lesions, although both studies have been small. Our results do not show such a dramatic cure rate (two out of seven, as opposed to six out of seven) but both studies showed improvement in all cases, using interferon. It is possible that improvement in administration of α-interferon may improve results, eg injection at the centre of the lesion might be better than at the periphery, where centrifugal drainage tends to diminish the concentrations of α-interferon most rapidly. Also, injections are painful and delivery by topical application would be preferable, if effective. Byrne *et al.*[5] have tried topical α-interferon gel with disappointing results. This may be because gel does not penetrate deeply enough into cervical tissue. One of the authors (AD) has therefore treated CIN with α-interferon mixed with dimethysulphoxide (DMSO) a penetrating agent, (unpublished case study), but this proved ineffective.

The incidental finding of the development of a new area of dysplasia in a part of the transformation zone not being treated with α-interferon demonstrated that there is likely to be heightened potential for malignant change in the whole of the transformation zone at the time of development of CIN in any part of it, and supports the current practice of treating the whole transformation zone when CIN occupies any part of it.

The complete disappearance of koilocytosis in α-interferon-treated patients raises the possibility of using α-interferon as used in this study for persistent cases of koilocytosis.

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References

1 Choo YC, Seto WH, Hsu C, Tany YH, Ma HK, Ng MH. Cervical intraepithelial neoplasia treated by perilesional injection of interferon. *Br J Obstet Gynaecol* 1986;93:372-9

2 Richart RM. The influence of diaguoide and therapeutic procedures on the distribution of cervical intraepithelial neoplasia. *Cancer* 1986;**19**:1635-8
3 McCance DJ, Campion MJ, Clarkson PK, Chesters PM, Jenkins D, Singer A. Prevalence of human papilloma virus type 16 DNA sequence in cervical epithelial neoplasia and invasive carcinoma of the cervix. *Br J Obstet Gynaecol* 1985;**92**:1101-4
4 Singer A, McCance DJ. The wart virus and genital neoplasia, a casual or causal association. *Br J Obstet Gynaecol* 1985;**92**:1083-5
5 Byrne MA, Moller BR, Taylor-Robinson D, *et al.* The effect of interferon on human papilloma virus associated with cervical intraepithelial neoplasia. *Br J Obstet Gynaecol* 1986;**93**:1136-44

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Forthcoming events

10th Congress of the European Association of Cranio-Maxillo-Facial Surgery
10-14 September 1990, Brussels, Belgium
Further details from: Mrs H van Leemputten, 10th Congress EACMFS, rue Joseph Stallaert 28, B-1180 Brussels, Belgium

5th European Symposium of International Physicians for the Prevention of Nuclear War: Health and Security 2000: New Thinking in Europe
13-16 September 1990, Coventry
Further details from: Symposium Secretariat, 601 Holloway Road, London N19 4DJ (Tel: 071 272-2020)

Uveitis & Retinal Frontiers: Diagnostic, Medical and Surgical Approaches to Uveitis and Retinal Diseases
14-16 September 1990, Carmel Valley Ranch Resort, California
Further details from: Extended Programs in Medical Education, Room C-124, University of California School of Medicine, San Francisco, CA 94143-0742, USA (Tel: 415 476-4251)

4th International Conference on Human Papillomaviruses and Squamous Carcinoma
16-19 September 1990, Chicago, Illinois
Further details from: Deene Alongi, 111 East Wacker Drive, Suite 600, Chicago, Illinois 60601, USA (Tel: 312 644 6610. Fax: 312 565 4658)

Selective Delivery of Therapeutic Polypeptides and Proteins
24-26 September 1990, Montreux, Switzerland
Further details from: Fiona Morgan, IBC Technical Services Ltd, Bath House, 56 Holborn Viaduct, London EC1A 2EX (Tel: 071-236 4080. Fax: 071-489 0849)

Gene Expression Under the Microscope: Recent Advances in In Situ Hybridisation
26-27 September 1990, Royal Society of Medicine, London
Further details from: (see previous entry)

Image Analysis in Microscopy: The Unbiased Picture
28 September 1990, Royal Society of Medicine, London
Further details from: (see previous two entries)

8th European Workshop on Clinical Neuropharmacology 27-29 September 1990
This meeting is devoted to parenteral neuropharmacology and treatment of movement disorders, spasticity and Parkinsonism in particular.
Further details from: Congress Office Tonne Verdonk, De Pinckart 54, 5674 CC Nuenen, The Netherlands

Hypnosis in the Therapy of Pain
6-7 October 1990, Verona, Italy
Further details from: Gualtiero Guantieri, Istituto 'H Bernheim', Via Valverde, 65-37122 Verona, Italy (Tel: 045 30795)

8th Postgraduate Course in Medical Mycology (Dermatomycology)
12-14 October 1990, University of California, San Francisco
Further details from: (see entry for 14-16 September 1990)

MRCP Part II Courses
15-19 October 1990, Royal Free Hospital, London
Further details from: Dr D Geraint James, Royal Free Hospital, Pond Street, London NW3 2QG (Tel: 071-794 0500)

The Skin from A to Z
20-21 October 1990, University of California
Further details from: (see entry for 14-16 September 1990)

39th Congress of the Brazilian Society of Coloproctology
20-24 October 1990, Pousada do Rio Quente, Goiás, Brazil
Further details from: Hélio Moreira, Av B, 435 setor oeste, Goiânia 74320, GO, Brazil (Tel: 062 224 3925. Fax: 062 241 6623)

Update on Thyroid Disease - 1990
2-3 November 1990, Hyatt Regency Embarcadero
Further details from: (see entry for 14-16 September 1990)

3rd International Academic Conference on Immunobiology in Otology, Rhinology and Laryngology
8-10 November 1990, Coronado, California
Further details from: Jan E Veldman, c/o Kugler & Ghedini Congresses, PO Box 516, NL-1180 AM Amstelveen, The Netherlands (Fax: +31 20 380 524)

The UCSF Otolaryngology Update: 1990
8-10 November 1990, San Francisco, California
Further details from: (see entry for 14-16 September)

4th Annual Facial Pain Conference: How to Recognise and Treat Difficult Facial Pain
16-17 November 1990, Eastman Dental Hospital, London
Further details from: Ms Pat Johnson, Student Administrator, Eastman Dental Hospital, Gray's Inn Road, London WC1X 8LD (Tel: 071-837 3646)

Environmental Health Risks and Responses
26-27 November 1990, Robin Brook Centre, St Bartholomew's Hospital, London
The aim is to review the ways in which man and other living things are exposed to toxicants, and consider the medical and biological consequences and the legal systems for regulating exposures
Applications by 5 October 1990
Further details from: The Education Department, BPMF, 33 Millman Street, London WC1N 3EJ (Tel: 071-831 6222: Fax: 071-831 7599)

3rd International Congress on Trace Elements in Medicine and Biology: Chromium and Trace Elements in Endocrinology
15-18 January 1991, Les Deux Alpes, France
Further details from: Arlette Alcaraz, Laboratoire de Biochimie C, CHRU de Grenoble, BP217 X, 38043 Grenoble Cedex, France (Tel: 76 42 81 21)