Oral Oncol, Eur J Cancer, Vol. 28B, No. 2, pp. 87–89, 1992
Printed In Great Britain

0964–1955/92 $5.00+0.00
Pergamon Press Ltd

Comments and Critique

Vitamin A Related Compounds in the Chemoprevention of Potentially Malignant Oral Lesions and Carcinoma

Crispian Scully and Peter Boyle

THE POSSIBILITY of non-invasive treatment of potentially malignant lesions of the oral mucosa has considerable appeal if an agent that was effective, safe and produced lasting benefit could be found. Vitamin A and related compounds are exciting interest in this respect and it is thus worth considering the evidence for their benefit.

Evidence has been accumulating to show that a low intake of vegetables and fruits is associated with an increased risk of oral and some other carcinomas [1–5]. The reason for the protective effect of a diet high in vegetables or fruits is unknown, but vitamin A and related compounds may be one factor [6]. Dietary beta-carotene (vitamin A precursor) does appear to reduce rates of epithelial neoplasms [7] and studies of serum levels of vitamin A in patients with head and neck carcinoma have shown low levels of retinoic acid-binding protein and vitamin A itself [8–12].

Beta-carotene is a natural precursor of vitamin A. Retinoids are the synthetic and natural analogues of vitamin A. There are many naturally occurring retinoids, including retinol, retinal, retinoic acid and their metabolites. Cellular retino-binding proteins [9] and retinoic acid-binding proteins [13] are found in normal oral and oropharyngeal mucosa and in higher amounts in carcinomas. Vitamin A and related compounds are well known to have pronounced physiological effects on differentiation in epithelia [14] and thus offer the chance of a physiological rather than a cytotoxic approach to the possibility of inhibiting, arresting or reversing the process of carcinogenesis. Is there any evidence of clinical benefit?

Vitamin A derivatives can indeed reverse the effects of carcinogens *in vivo* [15]. Retinoids can inhibit the development of experimental oral leukoplakia and carcinoma. 13-*cis*-retinoic acid [16, 17], retinyl acetate [18] and beta-carotene [19, 20] can all have tumour-suppressive activity in animal models of oral carcinogenesis. Unfortunately, however, though topical 13-*cis*-retinoic acid in some studies inhibited tumours induced in hamsters by 7,12-dimethylbenz(a)anthracene (DMBA), over half the animals died from hepatic and renal toxicity [21]. Others have failed to find a beneficial effect from 13-*cis*-retinoic acid [22]. Furthermore, though retinoids can suppress tumour development in animals exposed to carcinogens, neoplasia may appear on cessation of retinoid treatment [15, 23–25].

Human oral keratoses (leukoplakias)—some of which are potentially malignant—have also been successfully treated with systemic 13-*cis*-retinoic acid [26, 27], vitamin A [28–31], aromatic retinoids [32–34] and beta-carotene [35, 36]. Topical applications of vitamin A acid have also been effective in some studies [37].

In a study from the MD Anderson Institute, systemic 13-*cis*-retinoic acid (isotretinoin) produced some regression of oral leukoplakias but did not necessarily eradicate the lesions [27]. The study group of 44 subjects were randomly assigned to receive placebo (20 patients), or 13-*cis*-retinoic acid (24 patients) at 1–2 mg/kg per day for 3 months. The lesions regressed in 67% of those on the active drug (10% in the placebo group) and dysplasia was reversed in 54% of those on the drug (10% in the placebo group). Over half of the responders relapsed by 3 months after treatment ended but toxic effects were said to be acceptable to most patients.

A later study from the same group examined the effect of 13-*cis*-retinoic acid in cured head and neck cancer patients [38] and showed a significant reduction in second primary tumours. However, the toxicity of systemic 13-*cis*-retinoic acid at 50–100 mg/m^2 surface area was considerable and the results have yet to be confirmed by other workers. Some toxicity may be reluctantly acceptable in patients with an existing cancer but may be a severe restriction for use in those with only potentially malignant conditions.

A series of studies of oral leukoplakias conducted by the British Columbia Cancer Research Centre have shown benefit from systemic vitamin A and from beta-carotene. Tobacco/betel nut chewers from Kerala, India (21 patients) were given a short-term randomised trial of vitamin A 0.14 mg/kg weight for 6 months. There was complete clinical remission in 57% which was substantiated cytologically and histologically [27]. The same workers showed remission and inhibition of new oral leukoplakias in patients receiving vitamin A and beta-carotene, and in those receiving beta-carotene alone [28]. Regression was seen in 28% of those taking vitamin A and beta-carotene, and in 15% of those on beta-carotene alone.

After systemic vitamin A therapy for 6 months, the benefit extended up to a further 4 months though cellular chromatin

Correspondence to C. Scully, Centre for the Study of Oral Disease, University Department of Oral Medicine, Surgery and Pathology, Bristol Dental Hospital and School, Lower Maudlin Street, Bristol, BS1 2LY, U.K.; and P. Boyle is at the Division of Epidemiology and Biostatistics, European Institute of Oncology, Via Ripamonti 332/10, 20140 Milan, Italy.
Received 15 July 1992; accepted 17 July 1992.

patterns typical of leukoplakias could be seen on biopsy. The protective effect of the original treatments could be maintained for at least an additional 8 months by administering lower doses of vitamin A or beta-carotene [31].

In a study from another centre, beta-carotene given to patients with oral leukoplakia in a dose of 30 mg daily for 3 to 6 months also resulted in a 71% response rate in 24 patients, with no significant toxicity [36] but similar benefits from beta-carotene have not been found by others [39].

Unfortunately, the improvements in oral leukoplakia produced by treatment with the vitamin A related compounds used to date have not all be sustained and, more seriously, toxicity has been a common accompaniment of some treatments. Adverse reactions have included especially cheilitis, facial erythema, desquamation, conjunctivitis and photophobia, hypertriglyceridaemia, and liver damage. This toxicity has been the main limiting factor in the use of retinoids and there is also the possibility of teratogenicity.

Exactly how retinoids may act to inhibit carcinogenesis is unclear though some may enhance anti-tumour immune responses [21] and retinoids have a pronounced and essential effect on cell differentiation [40]. Retinoids may have an effect by their interaction with growth control mechanisms such as transforming growth factors [41] and thus also oncogenes such as the *jun–fos* complex [42], and possibly by acting on tumour suppressors either directly [43] or again via an interaction with transforming growth factors [44, 45].

Modulation of cellular differentiation and proliferation by compounds such as some of the newer retinoids thus offers the possibility for the therapeutic prevention, reversal, or arrest of carcinogenesis. The long-term results of other trials, including those using retinoids such as low dose 13-*cis*-retinoic acid [46], or 4-hydroxyphenyl retinamide [47], or those using natural vitamin A (retinyl palmitate) as in the EUROSCAN study of the EORTC [48, 49] are thus awaited with great interest, since these compounds are likey to have significantly less adverse effects than the earlier retinoids.

1. Graham S, Mettlin C, Marshall J, *et al.* Dietary factors in the epidemiology of cancer of the larynx. *Am J Epidemiol* 1981, **113**, 575–680.
2. Winn DM, Ziegler RG, Pickle LW, *et al.* Diet in the etiology of oral and pharyngeal cancer among women from the Southern US. *Cancer Res* 1984, **44**, 1216–1222.
3. Notani P, Jayant K. Role of diet in upper aerodigestive tract cancers. *Nutr Cancer* 1987, **10**, 103–113.
4. Ziegler RG. A review of epidemiologic evidence that carotenoids reduce the risk of cancer. *J Nutr* 1989, **119**, 116–122.
5 Boyle P, MacFarlane GJ, Zheng T, Maisonneuve P, Evstifeeva T, Scully C. Recent advances in epidemiology of head and neck cancer. *Curr Opinion Oncol* 1992, **4**, 471–477.
6. Marshall J, Graham S, Mettlin C, Shedd D, Swanson M. Diet in the epidemiology of oral cancer. *Nutr Cancer* 1982, **3**, 145–149.
7. Peto R, Doll R, Buckley JD, Sporn MB. Can dietary beta-carotene materially reduce human cancer rates? *Nature* 1981, **290**, 201.
8. Ibrahim K, Jafarey NA, Zuberi SJ. Plasma vitamin "A" and carotene levels in squamous cell carcinoma of the oral cavity and oropharynx. *Clin Oncol* 1977, **3**, 203–207.
9. Fex G, Wahlberg P, Biorklund A, Wennerberg J, Wilen R. Studies of cellular retinol-binding protein (CRBP) in squamous cell carcinomas of the head and neck region. *Int J Cancer* 1986, **37**, 217.
10. Ramaswamy PG, Krishnamorthy L, Rao VR, Bhargava MK. Vitamin and provitamin A levels in epithelial cancers. *Nutr Cancer* 1990, **14**, 273–276.
11. de Vries N, Snow GB. Relationship of vitamins A and E and beta carotene serum levels to head and neck cancer patients with and without second primary tumors. *Eur Arch Orl* 1990, **247**, 368.
12. Bichler E, Daxenbichler G, Marth C. Vitamin A status and retinoid-binding proteins in carcinomas of the head and neck region. *Oncology* 1983, **40**, 336–339.
13. Bichler E, Daxenbichler G. Retinoic acid-binding protein in human squamous cell carcinomas of the ORL region. *Cancer* 1982, **49**, 619–622.
14. Lippman SM, Kessler JF, Meyskens FL. Retinoids as preventive and therapeutic anticancer agents. Part 1. *Cancer Treat Rep* 1987, **71**, 391–405.
15. Mon RC, McCormick DK, Mehta RG. Inhibition of carcinogenes by retinoids. *Cancer Res* 1983, **43**, 5 (suppl), 2469s–2475s.
16. Shklar G, Marefat P, Kornhauser A. *et al.* Retinoid inhibition of lingual carcinogenesis. *Oral Surg* 1980, **49**, 325–332.
17. Shklar G, Schwartz J. Grau D, Trichler DP, Wallace KD. Inhibition of hamster buccal pouch carcinogenesis by 13-*cis*-retinoic acid. *Oral Surg* 1980, **50**, 45–52.
18. Burge-Bottenbley A, Shkar G. Retardation of experimental oral cancer development by retinyl acetate. *Nutr Cancer* 1983,**5**, 121–129.
19. Schwartz J, Suda D, Light G. Beta carotene associated with the regression of hamster buccal pouch carcinoma and the induction of tumor necrosis factor in macrophages. *Biochem Biophys Res Commun* 1986, **136**, 1130–1135.
20. Suda D, Schwartz JL, Shklar G. Inhibition of experimental oral carcinogenesis by topical beta carotene. *Carcinogenesis* 1986, **7**, 711–71.
21. Schwartz JL, Flynn E, Shklar G. The effect of carotenoids on the anti-tumour immune response *in vivo* and *in vitro* with hamsters and mouse immune effectors. *Ann NY Acad Sci (USA)* 1990, **587**, 92–109.
22. Gilmore W, Guinta JL. The effect of 13-*cis*-retinoic acid on hamster buccal pouch carcinogenesis. *Oral Surg* 1981, **51**, 256–265.
23. Slaga TJ, Fischer SM, Nelson K, Gleason GL. Studies on the mechanism of skin tumor promotion: evidence for several stages in promotion. *Proc Natl Acad Sci USA* 1980, 77, 3659–3663.
24. Sporn ML, Newton DL. Retinoids and chemoprevention of cancer: In: Zedeck MS, Lipkin M, Eds. *Inhibition of Tumor Induction and Development*. New York, Plenum Press 1981, 71–100.
25. Meyskens FL Jr, Goodman GE, Alberts DS. 13-*cis*-retinoic acid: pharmacology, toxicology, and clinical applications for the prevention and treatment of human cancer. *CRC Crit Rev Oncol Hematol* 1985, **3**, 75–101.
26. Shah JP, Strong EW, Decosse JJ, Itri LM, Sellers P. Effects of retinoids on oral leukoplakia. *Am J Surg* 1983, **146**, 466–470.
27. Hong WK, Endicott J, Itri LM, *et al.* 13-*cis*-retinoic acid in the treatment of oral leukoplakia. *N Engl J Med* 1986, **315**, 1501–1505.
28. Stich HF, Rosen MP, Hornby AP, Mathew B, *et al.* Remission of oral leukoplakias and micronuclei in tobacco/betal quid chewers treated with beta-carotene and with betacarotene plus vitamin A. *Int J Cancer* 1988, **42**, 195–199.
29. Stich HF, Hornby AP, Mathew B, *et al.* Response of oral leukoplakias to the administration of vitamin A. *Cancer Lett* 1988, **40**, 93–101.
30. Stich HF, Brunnemann KD, Mathew B, Sankaranarayanan R, Nair MK. Chemopreventive trials with vitamin A and beta-carotene: some unresolved issues. *Prev Med* 1989; **18**, 732–739.
31. Stich HF, Mathew B, Sankaranyarayanan R, Nair MK. Remission of precancerous lesions in the oral cavity of tobacco chewers and maintenance of the protective effect of beta-carotene or vitamin A. *Am J Clin Nutr* 1991, **53**, 298s–304s.
32. Koch HF. Biochemical treatment of precancerous oral lesions: the effectiveness of various analogues of retinoic acid. *J Maxfac Surg* 1978, **6**, 59–63.
33. Koch HF. Effect of retinoids on precancerous lesions of oral mucosa. In: Orfanos Ce, Brauno-Falco O, Farber EM, *et al.*, eds. *Retinoids: Advances in Basic Research and Therapy*. Berlin, Springer 1981, 307–312.
34. Cordero AA, Allevato MAJ, Barclay CA, Traballi CA, Donatti LB. Treatment of lichen planus and leukoplakia with the oral retinoid Ro10-0359. In: Orfanos CE *et al.* eds. *Retinoids*. Basel, Springer 1981, 273–278.
35. Garewal HS, Meyskens FL, Killen D. Response of oral leukoplakia to beta-carotene. *J. Clin Oncol* 1990, **8**, 1715–1720.

36. Garewal HS. Potential role of β-carotene in prevention of oral cancer. *Am J Clin Nutr* 1991, **53**, 294s–297s.
37. Schrey M, Esser E. Exfoliativ zytologie im verlauf der lakalbehandlung der intraoralen. Leukoplakie mit Vitamin-A-saure. *Dtsch Zahnartztl Z* 1978, **3**, 143–145.
38. Hong WK, Lippman SM, Itri LM, *et al.* Prevention of second tumours with isotretinoin in squamous cell carcinoma of the head and neck. *N Engl J Med* 1990, **323**, 795-801.
39. Anonymous. Beta-carotene didn't prevent cancer: what's up Doc? *J Natl Cancer Inst* 1990, **82**, 899–900.
40. Sporn MB, Roberts AB. Regulation of cell differentiation and proliferation by retinoids and transforming growth factor β. In: Burger MM, Sordat B, Zinkernagel RM, eds. *Cell to Cell Interaction* Basel, Karger 1990, 2–15.
41. Glick AB, Flanders KC, Danielpour D, Yuspa SH, Spron MB. Retinoic acid induces transforming growth factor β1 is mediated by the AP-1 complex. *Mol Cell Biol* 1990, **10**, 1392–1497.
42. Kim SJ, Angel P, Lafyatis R, *et al.* Autoinduction of transforming growth factor β1 is mediated by the AP-1 complex. *Mol Cell Biol* 1990, **10**, 1492–1497.
43. Mihara K, Cao X-R, Yen A *et al.* Cell cycle-dependent regulation of phosphorlation of the human retinoblastoma gene product. *Science* 1989, **246**, 1300–1303.
44. Laiho M, De Caprio JA, Luklow JW, Livingstone DM, Massague J. Growth inhibition by TGF-*B*1 linked to suppression of retinoblastoma protein phosphorylation. *Cell* 1990, **62**, 175–185.
45. Pietenpol JA, Stein RW, Moran E. *et al. TGF-*β1 inhibition of c-*myc* transcription and growth in keratinocytes is abrogated by viral transforming proteins with pRB binding domains. *Cell* 1990, **61**, 777–785.
46. Toma S, Mangiante PE, Margarino G, Nicolo G, Palumbo R. Progressive 13-*cis*-retinoic acid dosage in the treatment of oral leukoplakia. *Oral Oncol Eur J Cancer Part B*, 1992, **28B**, 121–123.
47. Chiesa F, Tradati N, Marazza M, *et al.* Prevention of local relapses and new localisations of oral leukoplakias with the synthetic retinoid Fenretinide (4-HPR). Preliminary results. *Oral Oncol Eur J Cancer Part B* 1992, **28B**, 97–102.
48. de Vries N, Van Zandwijk N, Pastorino U. The Euroscan study. *Br J Cancer* 1991, **64**, 985–989.
49. de Vries N, van Zandwijk N, Pastorino U. Chemoprevention in the management of oral cancer: EUROSCAN and other studies. *Oral Oncol Eur J Cancer Part B* 1992, **28B**, 153–157.