 DOI 10.1111/j.1365-2133.2006.07224.x

An evaluation of the efficacy of topical application of salicylic acid for the treatment of familial cylindromatosis

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Accepted for publication
15 December 2005

Key words
cylindroma, NF-κB, salicylic acid

Conflicts of interest
None declared.

Summary

Background Familial cylindromatosis is a rare genetic disorder, giving rise to neoplasms of the skin appendages. We have recently shown that loss of the cylindromatosis tumour suppressor gene leads to activation of NF-κB, a transcription factor having antiapoptotic activity. This provides a possible explanation for the deregulated growth of cylindromas. In cell-based assays, salicylate can prevent NF-κB activation caused by loss of the cylindromatosis gene, suggesting that salicylic acid application might be a potential treatment for cylindromatosis.

Objectives To assess the effectiveness of topical application of salicylic acid on familial cylindromas.

Methods Cylindromas in five patients from four different cylindromatosis families were treated with twice daily and then once daily topical salicylic acid. Clinical response was determined by serial tumour measurements.

Results In total 17 cylindromas in five patients were studied: 12 target lesions and five control lesions. The median size of the cylindromas was 1·0 cm (range, 0·6–2·8 cm). Two of the 12 cylindromas showed a complete remission. Another eight lesions showed some response, but not sufficient to qualify as partial remission. The control lesions remained stable or increased in size.

Conclusions Salicylic acid is a well-tolerated and potential new treatment for cylindromatosis.

Familial cylindromatosis (MIM 132700) is a rare autosomal dominant genetic predisposition to multiple neoplasms of the skin appendages. The incidence of familial cylindromatosis is low. In the Netherlands only four families with 45 affected individuals are known.[1] It is thought that the tumours (designated cylindromas because of their characteristic microscopic architecture, see Fig. 1b) develop from the apocrine sweat gland of the skin. In some cases large numbers of tumours on the scalp lead to the formation of a multinodular mass, sometimes referred to as 'turban tumour'. Cylindromas remain chromosomally stable and only rarely progress to a malignant tumour with metastatic potential.[2] Cylindromatosis causes considerable disfigurement and discomfort and, in severe cases, removal of the scalp and reconstruction using skin grafts is required. So far no effective noninvasive treatment has been reported.

The cylindromatosis tumour suppressor gene (*CYLD*) has been isolated[3] and is located on chromosome 16q.[4] *CYLD* has homology to the family of deubiquitinating enzymes and has been shown to possess ubiquitin protease activity *in vitro*.[5,6] Inactivating mutations in *CYLD* associated with cylindromatosis predict C-terminal truncations rendering the protein unstable or catalytically inactive. Recently we and others have reported that *CYLD* is a negative regulator of the I-κB kinase (IKK) complex, an upstream activator of NF-κB.[6–8] NF-κB is a transcription factor involved in inflammatory and immune responses, and its activation inhibits apoptosis in most tissues.[9,10] As a consequence, NF-κB is activated in a variety of human cancers.[7] In cell culture, loss of *CYLD* leads to hyperactivation of the IKKβ protein kinase, which in turn causes activation of NF-κB.[7] Based on these findings, we have proposed that in familial cylindromatosis loss of *CYLD* leads to enhanced NF-κB activity resulting in deregulated cell number homeostasis in sweat glands due to inhibition of apoptosis. Importantly, the IKKβ kinase, which is hyperactivated by loss of *CYLD*, can be inhibited by high doses of aspirin,[11] raising the possibility that aspirin might reverse (some of) the effects of loss of *CYLD*. Indeed, in several cell-based assays aspirin could compensate for loss of *CYLD*[7] (see Fig. 1a).

These observations raised the possibility that topical salicylate treatment could be a strategy to restore normal growth control in patients with familial cylindromatosis.[12,13] Topical application of salicylate is a well-established nontoxic treat-

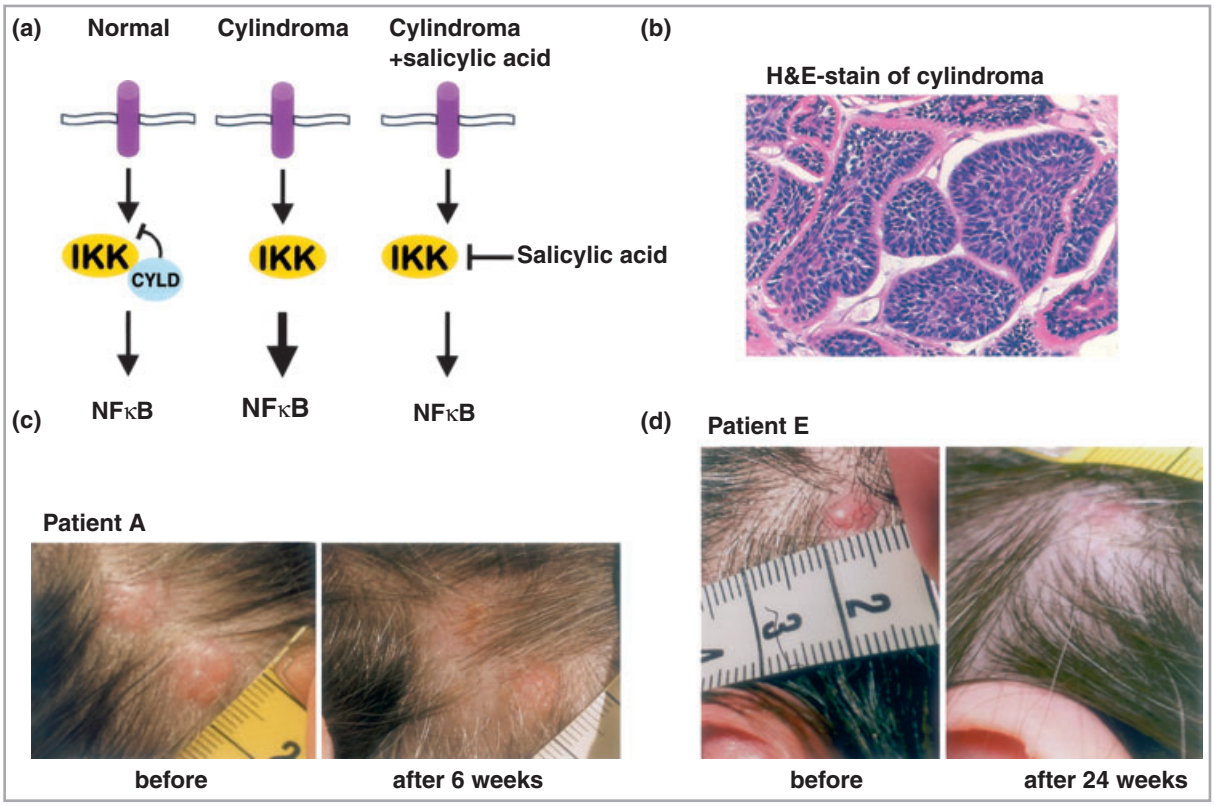

Fig 1. Effect of salicylic acid on the growth of cylindromas. (a) Suggested inhibitory action of salicylate on cylindromas. The cylindromatosis tumour suppressor gene (*CYLD*) acts as a negative regulator of I-κB kinase (IKK) activation, restricting NF-κB activity in normal cells. Loss of *CYLD* causes elevated NF-κB activity. Elevated NF-κB activity due to *CYLD* loss can be counteracted by IKK inhibition with salicylate. (b) Haematoxylin and eosin stain of cylindroma showing islands of cylindroma tissue from patient B (original magnification ×40). (c) Representative example of a complete (top left) and minimal response (bottom right) of a cylindroma after 6 weeks of topical application of salicylic acid. (d) Representative example of a minimal response after 24 weeks of topical salicylic acid application.

ment for many skin diseases.[14,15] We report here a pilot study in five familial cylindromatosis patients from four different families.

Patients and methods

Affected members of a family with cylindromatosis were eligible if they had a proven mutation in the *CYLD* gene and histologically confirmed cylindromas. All patients in this study were white female of Dutch decent. After receiving written informed consent, one to four cylindromas were chosen as target lesions and one cylindroma as a control lesion in each patient. The target lesions were treated with twice daily topical application of 20% acidum salicylicum in unguentum lanette for 6 weeks (100 g unguentum consists of: 15 g isopropylmyristaat, 25·5 g cera lanette SX, 21·25 g paraffine liquidem, 38·25 g vaseline with 50% salicylic acid). After 6 weeks, treatment was switched to application with *Collodium acidi salicylici* FNA 20% tincture (contents per gram: salicylic acid 200 mg, ether, ketonized ethanol and collodium with ricinus oil). Patients preferred the less greasy texture of the tincture. In addition, the collodium layer possibly enhances exposure of the cylindromas to salicylic acid. Responses were determined by measuring the longest diameter of the target lesion. Responses were defined according to the new guidelines to evaluate the response to treatment in solid tumours from the European Organization for Research and Treatment of Cancer[16] as follows: complete remission (CR), the disappearance of the target lesion; partial remission (PR), at least 30% decrease in the longest diameter of the target lesion, taking as reference the baseline longest diameter; progressive disease (PD), at least 20% increase in the longest diameter of the target lesion, taking as reference the smallest longest diameter recorded since the treatment started; stable disease (SD), neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD. This study was approved by the Institutional Review Board.

Results

Five patients from four different cylindromatosis families were enrolled in the study. In total 17 cylindromas were studied: 12 target lesions and five control lesions. The median size of the cylindromas was 1·0 cm (range, 0·6–2·8 cm). The topical application of salicylic acid was well tolerated. Side-effects consisted of a burning, slightly painful sensation for 15 min

Table 1 Effect of salicylate on the growth of cylindromas; responses encountered after 24 weeks of topical application of 20% salicylic acid

			Response					Response			
Patient	Follow-up (months)	Treated lesions	CR	PR	PD	SD	Control lesions	CR	PR	PD	SD
A	24	4	2	1	0	1	1	0	0	1	0
B	24	4	0	0	0	4	1	0	0	1	0
C	1·5	1	0	0	0	1	1	0	0	0	1
D	1·5	1	0	0	0	1	1	0	0	0	1
E	13	2	0	0	0	2	1	0	0	0	1

CR, complete remission: the disappearance of the target lesion; PR, partial remission: at least 30% decrease in the longest diameter of the target lesions, taking as reference the baseline longest diameter; PD, progressive disease: at least 20% increase in the longest diameter of the target lesion, taking as reference the smallest longest diameter recorded since the treatment started; SD, stable disease: neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD.

after application of both the cream and tincture. The cream could be used twice daily without any skin irritation. However, twice daily application of the tincture caused skin irritation with the risk of desquamation. It was therefore decided to apply the tincture only once a day, and this schedule was well tolerated.

After 6 weeks of treatment with 20% salicylic acid in unguentum lanette, all 12 cylindromas showed SD. Two patients (mother and daughter) were lost from follow-up at this point. The remaining patients then switched to treatment with 20% salicylic acid tincture. After a total treatment of 16 weeks one CR was encountered. After a total treatment time of 24 weeks a second CR was reached in the same patient; these two tumours remained in remission for over 1 year with sporadic use of salicylic acid (1 week per month, once daily application, Table 1). For patients B and E, in whom no CRs were obtained, we observed regrowth of the cylindromas when therapy was stopped for over 6 weeks. In total, eight of the 12 cylindromas treated with salicylic acid showed some response to treatment. They did not shrink much in diameter, but the height of the lesions decreased and the consistency became softer (see Fig. 1d). This latter observation was based on self-reporting by the patients and confirmed by the physician. Meanwhile, the control lesions remained stable or increased in size (Table 1).

Discussion

This pilot study demonstrates that topical application of salicylic acid is a well-tolerated treatment for cylindromatosis, which deserves further study. Importantly these results illustrate that insight into the basic molecular mechanisms underlying a disease, obtained in this case by a large-scale RNA interference study,[7] can lead to new therapeutic modalities. Based on these mechanistic insights into the function of the CYLD protein, one would have expected tumour shrinkage as a result of increased apoptosis. However, we have studied apoptosis in the responding lesions, but found no evidence of increased apoptosis as a result of salicylic acid therapy (data not shown). As tumour regression was a very slow process, this may have precluded detection of differences in apoptotic cells between treated and control lesions.

Responses to salicylic acid therapy varied, even within the same patient. Such variability may be caused by differences in skin penetration of the salicylic acid as a function of tumour size. Variability in responses may also be caused by modifier effects resulting from differences in genetic background of the patients. This is also suggested by the finding that the penetrance of the cylindromatosis phenotype is variable between patients. Furthermore, the nature of the mutation in the *CYLD* gene may influence response to therapy. However, the number of patients treated in this pilot study was too small to draw meaningful conclusions regarding these issues. After treatment of 12 target lesions in five patients from four different families, we encountered two CRs. A further eight treated cylindromas had some reduction in tumour volume, but this reduction was not sufficient to qualify as PR. Together, these data are encouraging enough to warrant further study into the efficacy of salicylic acid for the treatment of cylindromatosis. Salicylic acid therapy may not be a cure in most instances, but it may significantly reduce the frequency of surgical intervention in patients with cylindromatosis. In this context it should be noted that salicylic acid is a relatively poor inhibitor of IKKβ,[11] allowing only a partial and reversible inhibition of the NF-κB pathway. Recently developed more potent and specific IKK inhibitors might therefore be more suitable for the treatment of cylindromatosis inhibitors.[17,18] In addition, clinical trials could be considered to investigate the use of low-dose IKK inhibitors to prevent or delay the onset of the disease in young patients.

Acknowledgments

We thank the patients for participating in this study. We thank M.W. Bekkenk, M.H. Breuning, F.A. Beemer and S. Verhoef for referring patients to our Institute. This work was supported by grants from the Netherlands Organisation for Scientific Research (NWO) and the Danish Cancer Society and the Danish Medical Research Council to A.D. The funding agencies had no role in the study reported here.

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