Prolonged treatment with oral retinoids in adults: no influence on the frequency and severity of spinal abnormalities

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Summary
It is generally accepted that the spine is the site of predilection for retinoid-induced skeletal abnormalities. However, the reported prevalence of skeletal problems varies widely. To investigate the frequency and severity of retinoid-induced spinal abnormalities, all records of patients who underwent spinal radiographs at the request of the department of dermatology between 1983 and 1993 were reviewed. This group of 135 patients comprised the total population of retinoid-treated patients and those patients who were investigated for possible future retinoid treatment. The mean treatment period in the total group was 30 months and the mean cumulative dose of retinoid was 31 g. In 50 patients the treatment period was ≥ 24 months with 30 patients being treated for more than 48 months. Baseline radiographs were available from 26 patients and these were compared with the most recent X-rays during treatment. The mean treatment period in this 'prospective group' was 25 months and the mean cumulative dose of retinoid was 25 g.

The prevalence of diffuse idiopathic skeletal hyperostosis (DISH), degenerative changes and osteoporosis in the total group was respectively 16%, 53% and 29%. There was no statistically significant relation between the duration of treatment or the cumulative dose and the prevalence or severity of DISH, degenerative changes and osteoporosis. Only the age of the patients was significantly related to the frequency and severity of skeletal abnormalities. In the 'prospective group', again, no important changes were observed between the radiographs at baseline and during treatment.

In this study no relation whatsoever between spinal abnormalities and prolonged oral retinoid treatment could be established. The performance of annual routine spinal radiographs during retinoid treatment is not necessary in our opinion. Additional controlled and prospective studies on spinal and extraspinal skeletal abnormalities are required to develop definitive screening guidelines for patients submitted to long-term retinoid treatment.

During the last two decades, oral retinoids have acquired an indispensable place in the therapeutic arsenal of modern dermatology. The most notorious side-effects of oral retinoids, in adults as well as in children, are spinal- and extraspinal skeletal abnormalities. Retinoid-induced skeletal abnormalities resemble the symptoms described in chronic vitamin A intoxication. In adults the described abnormalities are highly identical to those of 'diffuse idiopathic skeletal hyperostosis' (DISH) and consist of spinal- and extraspinal hyperostosis (spurs) and calcification of tendons and ligaments. Other abnormalities include slender long bones and possibly osteoporosis. In children thickening of the periostium, bone resorption, disc narrowing and premature closure of the epiphyses have also been reported. The prevalence of retinoid-induced skeletal abnormalities, as mentioned in the literature, is widely variable. In Table 1 the population studies in adults (n ≥ 5) are summarized. In our department we have considerable experience with long-term retinoid treatment.

The aim of this study was to investigate the extent of retinoid-induced spinal abnormalities in a large patient population and to contribute to the development of screening guidelines for long-term retinoid treatment. The available spinal radiographs of our retinoid patients were studied with regard to the frequency and severity of DISH, degenerative changes and osteoporosis, using well-defined radiological criteria. The results were related to the duration of treatment, the cumulative
Table 1. Skeletal abnormalities following treatment with etretinate and acitretin in adults. Review of the literature (n ≥ 5)

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Study designa</th>
<th>Methodb</th>
<th>Retinoidc</th>
<th>Mean age (years)</th>
<th>Mean treatment period (months)</th>
<th>Mean daily dose (mg/kg)</th>
<th>% with skeletal abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson et al.⁷ (1988)</td>
<td>23</td>
<td>R</td>
<td>R/S</td>
<td>E</td>
<td>42</td>
<td>46</td>
<td>0.5</td>
<td>39</td>
</tr>
<tr>
<td>Montag et al.⁸ (1988)</td>
<td>11</td>
<td>R</td>
<td>R</td>
<td>E</td>
<td>25</td>
<td>75</td>
<td>32 mg/day</td>
<td>9</td>
</tr>
<tr>
<td>Halkier-Sorensen et al.⁹ (1989)</td>
<td>90</td>
<td>R</td>
<td>R</td>
<td>E</td>
<td>50</td>
<td>29</td>
<td>0.6</td>
<td>18</td>
</tr>
<tr>
<td>Gerber et al.¹⁰ (1984)</td>
<td>37</td>
<td>RC</td>
<td>R</td>
<td>E</td>
<td>41</td>
<td>&gt; 24</td>
<td>0.6</td>
<td>14e</td>
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<tr>
<td>D'Ignazio et al.¹¹ (1986)</td>
<td>38</td>
<td>RC</td>
<td>R</td>
<td>E</td>
<td>44</td>
<td>60</td>
<td>0.8</td>
<td>29</td>
</tr>
<tr>
<td>Melnik et al.¹² (1987)</td>
<td>8</td>
<td>RC</td>
<td>R</td>
<td>E</td>
<td>49</td>
<td>49</td>
<td>38 mg/day</td>
<td>100</td>
</tr>
<tr>
<td>Zeiger et al.¹³ (1990)</td>
<td>46</td>
<td>RC</td>
<td>R</td>
<td>E</td>
<td>50</td>
<td>53</td>
<td>0.5</td>
<td>41e</td>
</tr>
<tr>
<td>Gilbert et al.¹⁴ (1986)</td>
<td>8</td>
<td>P</td>
<td>R</td>
<td>E</td>
<td>51</td>
<td>11</td>
<td>0.5–1.2</td>
<td>0</td>
</tr>
<tr>
<td>Kilcoyne et al.¹⁵ (1988)</td>
<td>240</td>
<td>P</td>
<td>R</td>
<td>A</td>
<td>12–24</td>
<td>10–75 mg/day</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Török et al.¹⁶ (1989)</td>
<td>15</td>
<td>P</td>
<td>S</td>
<td>E</td>
<td>33</td>
<td>4</td>
<td>0.7–1.0</td>
<td></td>
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<tr>
<td>Mork et al.¹⁷ (1992)</td>
<td>45</td>
<td>P</td>
<td>R/S</td>
<td>A</td>
<td>48</td>
<td>24</td>
<td>0.5</td>
<td>13</td>
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<tr>
<td>Hohl et al.¹⁸ (1992)</td>
<td>16</td>
<td>P</td>
<td>R</td>
<td>A</td>
<td>46</td>
<td>11</td>
<td>0.4</td>
<td>6</td>
</tr>
<tr>
<td>Kullavanijaya et al.¹⁹ (1993)</td>
<td>16</td>
<td>P</td>
<td>R</td>
<td>A</td>
<td>28</td>
<td>12</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

a R = retrospective; RC = retrospective controlled; P = prospective.
b R = radiography; S = scintigraphy.
c E = etretinate; A = acitretin.
d 39 patients etretinate; 4 patients isotretinoin; 3 patients arothenoidethylester (Ro–6298).
e Difference patients—controls not significant.
f Difference patients—controls significant (P < 0.001).
dose and the age of the patient. Pretreatment radiographs were available in 26 patients and these were compared with the most recent X-rays during treatment.

Methods

The records of all patients who underwent spinal radiographs on request of the department of dermatology during the period 1983–93 were reviewed. Radiographic examination of the spine is part of our protocol for oral retinoid treatment. Patients who underwent pretreatment screening were also included in the study. The duration of treatment and the cumulative dose of etretinate and acitretin were calculated in each patient. For all calculations we chose as the reference point the time of the most recent radiographic survey. From the total group a ‘prospective group’ was identified who had had pretreatment radiographs as well as one or more X-ray surveys during retinoid therapy and who had had a minimal treatment period of 9 months.

Both the available pretreatment radiographs and the most recent radiographs of each patient (anterior–posterior as well as lateral views) were evaluated by the same radiologist (JAML). The radiographs were reviewed in arbitrary sequence and in chronological order for each patient. The radiologist was unaware of details from the patient’s records. The vertebral levels C3–C7, Th3–Th12 and L1–S1 of all radiographs were investigated for osteophytes (small, medium or large), syndesmophytes (1/3, 2/3 or 3/3 bridging), osteoporosis, narrowing of the intervertebral discs and ligament calcification. Triangular outgrowths located several millimetres from the edge of the vertebral bodies were defined as osteophytes and vertical outgrowths extending from the edge of one vertebral body to the next were defined as syndesmophytes. 

DISH was diagnosed when the spinal radiographs showed a flowing ligament calcification and syndesmophytes along the anterior aspect of at least three vertebral bodies, a relative preservation of intervertebral disc height in the involved vertebral segment and the absence of osseous fusions. Osteophytes and narrowing of the intervertebral discs were defined as degenerative changes. Beside a ‘yes or no’ classification of DISH, degenerative changes and osteoporosis, total severity scores for DISH and degenerative changes were defined for each reviewed spinal radiograph. To compute the severity of DISH (0–84 points), syndesmophytes with an extension of less than one-third of the intervertebral disc height scored 1 point per vertebral level, syndesmophytes with an extension between one-third and two-thirds scored 2 points per vertebral level and, when more than two-thirds of the intervertebral disc height was involved, the score was 3 points per vertebral level. Ligament calcification was scored with 1 point per vertebral level. To compute the severity score of degenerative changes (0–84 points), small, medium or large osteophytes were scored with respectively 1, 2 or 3 points per vertebral level and disc narrowing was scored with 1 point per vertebral level. Osteoporosis was assessed only as present or absent. A severity score was not used, as plain radiography is considered an inaccurate method to evaluate the severity of osteoporosis. The prevalence and the severity scores of DISH, degenerative abnormalities and osteoporosis in the pretreatment situation were compared with the most recent radiographs during retinoid treatment. Possible dependencies of the prevalence of DISH, degenerative changes and osteoporosis on the one hand on duration of treatment, cumulative dose and age on the other hand were investigated using stepwise logistic regression with the latter three parameters as independent variables. The relationship between the severity scores of DISH and degenerative changes and duration of treatment, cumulative dose and age was investigated using Spearman’s rank correlation coefficient.

Results

Patients

The spinal radiographs of 135 patients (81 men and 54 women) were studied. The mean age of the patients was 46 years. The population consisted of 77 patients with psoriasis, 31 patients with a monogenic disorder of keratinization, six patients with lichen planus, five patients with cutaneous lupus erythematosus, four patients with mycosis fungoides, three patients with pityriasis rubra pilaris and nine patients with other chronic hyperkeratotic skin diseases. The mean treatment period in the total group was 30 months (0–200 months) and the mean cumulative dose was 31 g (0–230 g). In 50 patients the treatment period was ≥ 24 months; 30 patients were treated for more than 48 months.

Prevalence of diffuse idiopathic skeletal hyperostosis, degenerative changes and osteoporosis

The prevalence of DISH, degenerative changes and osteoporosis in the total group was, 16%, 53% and
29\%, respectively. No statistically significant relationship between these prevalences and the duration of treatment of the cumulative dose could be shown. In using stepwise logistic regression, it appeared that the only significant relation of each of these three parameters that could be established was that with the age of the patients. This dependency is best shown by computing the prevalence of DISH, degenerative changes and osteoporosis for different age classes (Table 2).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>&lt; 35</th>
<th>35-45</th>
<th>45-55</th>
<th>55-65</th>
<th>&gt; 65</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>36</td>
<td>29</td>
<td>23</td>
<td>32</td>
<td>15</td>
<td>135</td>
</tr>
<tr>
<td>DISH (%)</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>38</td>
<td>33</td>
<td>16</td>
</tr>
<tr>
<td>Degenerative changes (%)</td>
<td>19</td>
<td>52</td>
<td>52</td>
<td>81</td>
<td>80</td>
<td>53</td>
</tr>
<tr>
<td>Osteoporosis (%)</td>
<td>14</td>
<td>21</td>
<td>15</td>
<td>38</td>
<td>53</td>
<td>29</td>
</tr>
</tbody>
</table>

DISH, diffuse idiopathic skeletal hyperostosis.

Severity scores of diffuse idiopathic skeletal hyperostosis and degenerative changes

The mean severity scores for DISH and degenerative changes were 2.0 (0–41 points) and 2.8 (0–38 points), respectively. There was no significant correlation (Spearman's rank correlation coefficient) between the severity scores of DISH (Fig. 1) and degenerative changes and the duration of treatment or the cumulative dose. The correlation coefficients of the severity scores of DISH and degenerative changes with age.
however, appeared to be highly significant: \( r = 0.39 \) (\( P < 0.01 \)) for DISH and \( r = 0.61 \) (\( P < 0.01 \)) for degenerative changes.

‘Prospective group’

In the ‘prospective group’ (\( n = 26 \)), the mean duration of treatment was 25 months (9–61 months). The mean cumulative dose was 25 g (6.6–61.2 g). Before treatment two of 26 patients had DISH vs. four of 26 patients during treatment. The two patients who developed DISH during treatment had treatment periods of 14 and 29 months. Their severity score was only 4 points (maximum DISH score 84 points). Before retinoid treatment 14 of 26 patients had degenerative changes; during treatment 15 of 26 patients. Osteoporosis was diagnosed in nine of 26 patients before treatment and in 10 of 26 patients during treatment. These differences were too small to be meaningfully analysed statistically.

The two patients with DISH before treatment did not show any progression during treatment (treatment period 10 and 12 months). Three of the 14 patients with degenerative changes before treatment showed a slight progression (1–2 points) of the severity score during treatment (treatment period 14, 19 and 53 months).

Discussion

Many reports have appeared in the recent literature on retinoid-induced skeletal abnormalities (Table 1). However, no consensus has been reached on the frequency and magnitude of these side-effects. Most of the communications are anecdotal, the population studies are predominantly uncontrolled, and prospective studies on prolonged treatment with oral retinoids are not available. A major problem in these studies is the differentiation of retinoid-induced from age-induced bone changes. The reported prevalence of DISH in the normal population varies from 2-6 to 28%. It is very complicated to conduct an extensive placebo-controlled study for practical and ethical reasons. Furthermore, there is no consensus on the definitions of the kind and severity of retinoid-induced spinal abnormalities. In the present study we used the definitions that are now generally accepted in the radiological world. The design of the present study is retrospective, concerning the spinal abnormalities of our retinoid population and of those patients who underwent pretreatment X-ray screening. This approach provided the opportunity to relate the frequency and severity of the various spinal abnormalities to the duration of treatment, the cumulative dose and the age of the patients. As this could be a possible reason for bias, it is important that not a single patient was excluded from retinoid treatment because of pre-existing skeletal abnormalities. The mean age of the patients in relation to the duration of treatment showed a rather homogeneous distribution and all patients suffered from severe psoriasis or other disorders of keratinization. The present study is extensive (135 patients), especially in comparison with the available reports in the literature (Table 1) and includes a ‘prospective’ sample of 26 patients. A mean duration of treatment of 30 months and a mean cumulative dose of 31 g are considerable, 50 patients were treated for more than 24 months and 30 patients for more than 48 months. Another advantage of this study is the fact that the results concern all retinoids used by the patients, so that possible bias induced by retinoid treatment in the past is avoided. The conclusion which is reached from the data presented in this communication is simple and clear. There was no relation whatsoever between the duration of retinoid treatment or the cumulative dose and the prevalence and severity of DISH, degenerative changes and osteoporosis. The only significant variable in this respect was the age of the patients. Owing to the inconsistency of diagnostic criteria used in the literature, it is not possible to provide a concise comparison of our results with those reported by other authors (Table 1).

These results do not permit us to draw definitive conclusions, but we would like to suggest that spinal abnormalities due to oral retinoid treatment only occur sporadically in predisposed subjects. DISH has been described as ‘an extremely common’ entity in the general population and spinal \( \text{s} \), as described in the literature, are probably more a normal variation than a complication of retinoid treatment.

There is no consensus on the guidelines for routine surveillance of patients during prolonged retinoid treatment, recommendations in the literature diverge from no X-ray screening at all to pretreatment and annual screening of spinal areas. Several authors recommend additional screening of extraspinal areas. The present study does not lend support to the performance of annual routine spinal radiographs during retinoid treatment. It is important to ask for skeletal pains and mobility restriction on a regular basis during oral retinoid treatment and to focus on both spinal and extraspinal regions.

Additional controlled and prospective studies are
required to develop definitive screening guidelines for patients submitted to long-term oral retinoid treatment. Further investigations should be focused on the basic mechanisms and specific locations of retinoid-induced bone changes and on defining high-risk patients in this respect.

References