Haugeberg et al recently published clinical decision rules to identify patients with rheumatoid arthritis (RA) at risk for osteoporosis. Included were patients treated with glucocorticoids, a subject that has been for a long time the interest of rheumatologists.

For example, the Dutch Society for Rheumatology has recently published guidelines for the prevention of glucocorticoid induced osteoporosis (GIOP). This document was prepared by a group of rheumatologists of the society and other experts to mark the occasion of the publication of the 3rd Osteoporosis Guideline, (the “CBO consensus”) which was, in turn, prepared at the request of the Dutch authorities by a multidisciplinary group who examined evidence based medicine.

Figure 1 is a stream diagram showing the diagnostic and therapeutic steps in making decisions for the prevention of GIOP. Factors that influence this decision include the dose of glucocorticoids and the presence of other risk factors such as age, sex, previous fracture, and bone mineral density (BMD). The main message is that treatment with bisphosphonates should be started immediately in patients at high risk (high dose of glucocorticoids, prevalent fracture, postmenopausal women, and elderly men).

The recommendations cover some uncertainties. Firstly, it is unclear what is the threshold value of BMD below which prevention is indicated if the intake of glucocorticoids is, for example, 7.5 mg prednisone equivalents/day in the absence of other risk factors. The CBO consensus suggested a T score \(-2.5\) or a Z score \(-1\). However, other groups have suggested different thresholds. The UK consensus group suggested a T score \(-1.5\) and the American College of Rheumatology suggested a T score \(-1\). The main reason for the absence of consensus is the uncertainty that the risk for osteoporosis is increased in a low risk group treated with low dose glucocorticoids, that fractures can be prevented in this group and, perhaps most relevant, that the fracture threshold is altered in GIOP. Indeed, bone loss is limited in patients chronically treated with low dose glucocorticoids if calcium and vitamin D supplements are given.

Secondly, it is still unclear if these patients should have an x-ray examination of the spine to document vertebral deformities. Although only one in three vertebral deformities is accompanied by acute symptoms of fractures, it has been recently shown that non-clinically manifest vertebral deformities also result in increased morbidity and an increased risk for new fractures. Introducing a new risk factor is a reason for increasing awareness: starting glucocorticoid treatment should be accompanied by treatment with bisphosphonates in high risk patients and by dual energy x-ray absorptiometry (DXA) measurement in others.

Thirdly, specific risk factors of bone loss in conditions such as RA were not considered. Accelerated bone loss has been documented in patients with RA with high disease activity, immobility, and low body weight. However, no studies are available on the prevention of osteoporosis in patients with RA with these risk factors, and, thus, this information was lacking in the guidelines.

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Stream diagram

- Start glucocorticoids
- Look for special circumstances
- General advice
- Dose and fracture anamnesis
  - High dose (>15 mg/day) or fracture
  - Intermediate dose (7.5-15 mg/day)
  - Low dose (<7.5 mg/day)
- Postmenopausal women
  - Men > 70 years
- Start bisphosphonate
- High risk
- DXA x Ray spine
- 1-3 years
- Low risk

Figure 1 Stream diagram for osteoporosis prevention in GIOP.
In conclusion, the guidelines on the prevention of GIOP, which have been approved by the Dutch Society for Rheumatology, should increase awareness about patients at high risk. The publication by Haugeberg et al. draws our attention to patients with RA who are not treated with glucocorticoids who perhaps also should be a target for prevention of bone loss and osteoporosis. This proposal needs to be fully explored in future studies. Thus, guidelines may disclose not only our knowledge in specific clinical situations but also may open up areas for new research.

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REFERENCES

Does long term treatment with azathioprine predispose to malignancy and death in patients with systemic lupus erythematosus?

P Nero, A Rahman, D A Isenberg

The treatment of patients with rheumatic diseases with second line agents has expanded in the past three decades. However, such drugs have been linked with the development of malignancy, particularly in patients with rheumatoid arthritis.1 Azathioprine is used to treat patients with systemic lupus erythematosus (SLE) with renal disease, but also may open up areas for new research.
patients with SLE. In rheumatoid arthritis and in Sjögren's syndrome, however, it has been linked with lymphoma development.1,14

We conclude that although azathioprine seems to be a safe second line agent for the treatment of patients with SLE larger and longer term studies are needed to confirm these findings.

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Bone mineral density in patients with systemic sclerosis
B Frediani, F Baldi, P Falsetti, C Acciai, G Filippou, A Spreafico, F Chellini, C Capperucci, P Filipponi, M Galeazzi, R Marcolongo

Generalised radiological osteopenia has been seen to occur in a significant percentage of patients with systemic sclerosis (SSc).1,2 Bone mineral content was found to be reduced at the radius,6,7 lumbar spine, and the total body.7 No data are available on quantitative ultrasound (QUS) evaluation of bone in patients with SSc.

PATIENTS AND METHODS
In this study, bone mineral density (BMD) and stiffness index (SI) were measured in patients with SSc not treated with steroids to investigate the presence of systemic osteoporosis.

Forty seven women (mean age 53.9 years (range 32–77)) affected with SSc were investigated: 20 were premenopausal (preSSc) and 27 postmenopausal (postSSc). All the patients satisfied the preliminary American Rheumatology Association criteria indicated in the classification of progressive SSc.

The control group consisted of 50 healthy female subjects: 23 premenopausal (prenorm) and 27 postmenopausal (postnorm). The exclusion criteria were treatment with corticosteroids, immunosuppressant drugs, hormone replacement therapy, thyroxine, and bone regulating drugs and the presence of demineralising diseases.

A detailed history was taken of each patient, with particular reference to age, menopausal status, disease duration, current or previous treatments, and current or previous diseases; their height and weight were measured and related by the body mass index ratio. There were no significant differences between groups. The following serological markers were determined: antinuclear antibodies, anticentromere antibodies, anti-extractable nuclear antigen, including anti-Scl70, -Sm, -RNP, -SSB, -SSA, and Jo-1.

Examinations were also carried out to determine the extent of any internal organ involvement. The patients were divided into three groups based on the extent of cutaneous involvement: limited, intermediate, and diffuse. BMD (total body, lumbar spine, and femur neck) was evaluated by fan beam x ray Lunar Expert, version 1.72. The SI (derived from broadband ultrasound absorptiometry and speed of sound) was evaluated by quantitative ultrasonometry of the heel using the Lunar Achilles Plus. T scores (the difference between the BMD of the patients and that of young healthy adults corrected for the standard deviation) were used in dual x ray absorptiometry and QUS.

RESULTS
The results of this study show that bone mass was reduced in patients with SSc. BMD, expressed in g/cm², was significantly less in the SSc subgroups than in controls (lumbar spine BMD: 1.309 prenorm v 1.159 preSSc, p<0.05; 1.193 postnorm v 0.952 postSSc, p<0.01; neck femur BMD: 1.010 prenorm v 0.938 preSSc, p<0.05; 0.904 postnorm v 0.816 postSSc, p<0.01; stiffness: 100.0 prenorm v 72.0 preSSc, p<0.05; 91.0 postnorm v 78.2 postSSc, p<0.05). T scores were lower in the SSc subgroups than in controls. The reduction in bone mass was more marked in the lumbar spine and heel. It is known that these two sites are, respectively, partially and completely trabecular. SSc related osteoporosis thus seems to have the typical characteristics of postmenopausal osteoporosis.

Many studies suggest that QUS is useful in investigating bone quality.1 In our patients the prevalent impairment of stiffness at the heel also provided an additional indication for the presence of a qualitative alteration in the trabecular microarchitecture. BMD and SI were reduced in women with the diffuse form of skin involvement and in women with one or more internal organs affected (table 1). A previous study reported that bone mass was related to the extent of skin involvement but did not evaluate the extent of visceral involvement.3 Many authors

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Table 1 Number of deaths and malignancy in patients with SLE treated with azathioprine

<table>
<thead>
<tr>
<th>Azathioprine (years of treatment)</th>
<th>n</th>
<th>Died (No [%])</th>
<th>Lost to follow up (No [%])</th>
<th>Malignancy (No [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>38</td>
<td>5 (13)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1-4</td>
<td>55</td>
<td>10 (18)</td>
<td>2 (4)</td>
<td>8 (15)</td>
</tr>
<tr>
<td>5-9</td>
<td>40</td>
<td>11 (28)</td>
<td>0</td>
<td>3 (8)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>15</td>
<td>1 (7)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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Between 1 and 4 years and 3 for between 5 and 9 years. The two patients lost to follow up had been receiving azathioprine treatment for 3 and 4 years at that time.

We have been unable to locate any publications examining azathioprine related complications in the treatment of patients with SLE.
suggest that the extent of skin involvement is directly related to the extent of visceral involvement and to the severity of the disease.\textsuperscript{8–10}

In the patients as a whole, a logistical model was prepared in which the presence of osteoporosis (a T score below $-2.5$) in at least one skeletal site was the dependent variable. In this model the age of the subject, years since menopause, and body mass index were all significantly associated with osteoporosis.

In conclusion our data suggest that bone mass, bone density, and bone quality are altered in patients with SSc with the diffuse form of skin disease and/or at least one internal organ affected.

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**Table 1** Bone mineral density (g/cm$^2$) in women with SSc categorised according to the extent of disease

<table>
<thead>
<tr>
<th>Cutaneous disease</th>
<th>Internal organs affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Limited (n = 15)</td>
<td>Intermediate (n = 14)</td>
</tr>
<tr>
<td>Total body</td>
<td>1.104 (0.088)</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>1.038 (0.161)</td>
</tr>
<tr>
<td>Femur neck</td>
<td>0.831 (0.112)</td>
</tr>
<tr>
<td>Os calcis</td>
<td>89 (13.7)</td>
</tr>
</tbody>
</table>

*$p<0.05$ (SSc v control); **$p<0.01$ (SSc v control)

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**REFERENCES**

PostScript

MATTERS ARISING

Treatment of resistant giant cell arteritis with etanercept
Tan et al recently described a case of “resistant giant cell arteritis” successfully treated with etanercept. Their patient, who had classical symptoms of polymyalgia rheumatica (PMR), developed headaches while receiving low dose steroids. Biopsy of a temporal artery showed no arteritis. Because giant cell arteritis (GCA) was suspected on clinical grounds, high dose steroids were instituted. Six months later, despite continued steroid treatment, a transient ischaemic attack (TIA) involving right arm weakness occurred, which was ascribed to “arteritis (sic)”. An insufficiency fracture ensued. As the erythrocyte sedimentation rate and C reactive protein were persistently raised, a diagnosis of GCA resistant to treatment was made, and etanercept was given. The acute phase reactants normalised, and the symptoms referable to PMR resolved fully reducible the levels of cytokines that drive the acute phase response in GCA, thus ameliorating constitutional symptoms and signs, this treatment may not mitigate the disease’s most feared consequence—namely, ischaemia leading to visual loss. As demonstrated by elegant work over the past decade by Weyand and Goronzy, ischaemia in GCA results from an array of other cytokines with pathogenic potential—for example, platelet derived growth factor and vascular endothelial growth factor, which would be unaffected by TNFα’s blockade.

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References

Authors’ reply
We thank Dr Dockens for his comments on the difficulty in the diagnosis, treatment, and classification of polymyalgia rheumatica (PMR) and giant cell arteritis (GCA). However, the sole purpose of our case report was to show how etanercept might have a role in the treatment of resistant disease of the PMR/GCA spectrum. From a clinical standpoint we are happy to label our patient as having GCA (in addition to PMR) based on his headaches, constitutional abnormalities, temporal tenderness, and resistance to 15 mg of prednisolone a day. We know that the disease was resistant because his symptoms and laboratory abnormalities persisted despite continued use of relatively high dose steroids, and there was clinical deterioration mirrored by an increase of the acute phase response.

Of course it is entirely possible that his transient ischaemic attack was related to atheroma, even in the face of very active GCA, but a rare arteritic related event could not be excluded in the clinical circumstances. The adverse effect of high dose steroids on blood pressure and lipid profiles and their association with atheromatous related disease was an additional concern about their continued use. We agree that it would be folly to treat patients on the basis of a raised erythrocyte sedimentation rate (ESR) alone but an extremely high ESR virtually invariably signifies disease flare. Activation of the inflammatory cascade has a pivotal role in the pathogenesis of GCA so it seems logical that anti-tumour necrosis factor treatment could abrogate this regardless of the other cytokine mediators of disease.

Fifteen months after the original case report the clinical diagnosis remains the same and the patient continues to experience flares in disease with tapering of the steroid dose below 5 mg/day.

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Fenofibrate and losartan
The leader by Professor Bardin makes an excellent point. We could benefit from the hypouricoacemic action of drugs that are not licensed for this use (for example, losartan and fenofibrate).

Other drugs in common use may also have a uricosuric effect. For example, atorvastatin can reduce serum uric acid concentrations in patients with peripheral atherosclerosis disease or hyperlipidaemia.4 However, the mechanisms involved are not clear cut; we speculate that atorvastatin can increase renal blood flow and decrease serum creatinine levels.4 Thus, the Medical Research Council/British Heart Foundation Heart Protection Study (HPS) showed that simvastatin decreased the deterioration of the glomerular filtration rate (GFR) over a period of 4.6 years in high risk patients with (n = 5863) it without (n = 14 573) diabetes.3 This effect on GFR would almost certainly influence urate excretion. These statin mediated effects are relevant because, as Professor Bardin points out, patients with hyperuricaemia may also be dyslipidaemic.

Closely to the interests of rheumatologists are the non-steroidal anti-inflammatory drugs (NSAIDs). Some NSAIDs may exert a favourable effect on urate excretion. For example, diflunisal has been reported to have a uricosuric effect, although the inhibition of xanthine oxidase activity has also been proposed.5 Azapropazone (not used as a first line option) has been shown in lower serum urate levels.6 Indomethacin may have uricosuric properties.7 Tiaprofenic acid

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1–3%.
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is another NSAID with hypouricaemic effect.\textsuperscript{7} Aspirin has a bimodal effect on the renal handling of uric acid. High doses (\textgtr3 g/day) are uricosuric, while lower doses (1–2 g/day) cause urate retention.\textsuperscript{8} At the lowest dose (75 mg/day) aspirin caused a 15% decrease in urate excretion with a slight but significant increase in serum urate levels.\textsuperscript{9}

The clinical significance of these “additional” uricosuric effects remains to be established. There is also a need to assess the value of using combinations of these drugs (for example, losartan and fenofibrate together with an NSAID with beneficial effects on urate excretion).

The search for NSAIDs that do not exert renal toxicity may well be worthwhile because of their widespread use. Acute attacks of gout are usually treated with high doses of NSAIDs. It could be useful to have NSAIDs with uricosuric properties as well as the analgesic and anti-inflammatory effect.

References


Notice

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Forthcoming Events

International Congress on SLE and Related Conditions
9–13 May 2004; New York, New York, USA
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Fax: +1 615 322 2784
Email: Lupus2004@theoakleygroup.com
Website: http://www.lupus2004.org

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1OF Servier Young Investigator Fellowship: 40 000
Contact: Congress Secretariat at info@osteofound.org
Website: www.osteofound.org

International Society for the Study of the Lumbar Spine
31 May–3 June 2004; Porto, Portugal
Contact: International Society for the Study of the Lumbar Spine, 2075 Bayview Avenue, Room MG 323, Toronto, Ontario, Canada M4N 3M5
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Fax: 00 1 416 480 6055
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8th EULAR Sonography Course
7–9 June 2004; Berlin, Germany
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Website: www.eular.org

First European Course: Capillaroscopy and Rheumatic Diseases
10–12 September 2004; Genova, Italy
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Xth International Conference on Behcet’s Disease
27–31 October 2004; Antalya, Turkey
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