Prevention of glucocorticoid osteoporosis: a consensus document of the Dutch Society for Rheumatology

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Haugeberg *et al* recently published clinical decision rules to identify patients with rheumatoid arthritis (RA) at risk for osteoporosis.¹ Included were patients treated with glucocorticoids, a subject that has been for a long time the interest of rheumatologists.^{2–4}

For example, the Dutch Society for Rheumatology has recently published guidelines for the prevention of glucocorticoid induced osteoporosis (GIOP).⁵ 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.⁶

Figure 1 is a stream diagram showing the diagnostic and therapeutic steps in making decisions for the prevention of GIOP.⁵ 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 <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 <−1.⁶ However, other groups have

suggested different thresholds. The UK consensus group suggested a T score <−1.5⁷ and the American College of Rheumatology suggested a T score <−1.³ 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.⁸ Indeed, bone loss is limited in patients chronically treated with low dose glucocorticoids if calcium and vitamin D supplements are given.⁹

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.^{10 11} 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,¹² immobility, and low body weight.¹³ 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.

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

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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, or as a steroid-sparing agent.² We have assessed the risk that azathioprine treatment predisposes to the development of malignancies and death in patients with SLE.

We carefully reviewed the case notes of 358 patients with SLE receiving long term follow up in the Lupus Clinic at University College London, between 1978 and 2002, and assessed their treatment. Three hundred and twenty six (91.1%) patients were female and 32 (8.9%) male. One hundred and forty eight (41.3%) were treated at any time with azathioprine, while 210 (58.7%) never used this second line agent. The mean (SD) ages of the users and non-users were similar (40.5 (12.7) v 45.3 (13.2), respectively, which is not significant by χ^2 test with 95% confidence intervals). The mean (SD) duration of azathioprine treatment was 3.8 (3.9)

years (minimum of 6 months and maximum of 18 years). Most patients are alive (83.2%) and only a minority were lost to follow up (3.1%). Forty nine (13.7%) of our patients have died: 27/148 (18%) had received azathioprine and 22/210 (10%) had not. Eight of our patients prescribed azathioprine developed a malignancy (none had a lymphoma), whereas 14 not given azathioprine have done so (three had lymphomas: one non-Hodgkin and two Hodgkin). These differences are not statistically significant (χ^2 test). However, the number of deaths in the azathioprine group which is almost double that in the other group does raise concerns, although it may simply be identifying a subgroup with more serious disease.

Table 1 shows the number of malignancies and death in patients with SLE treated with azathioprine, according to the duration of treatment.

Five of the patients who died were receiving azathioprine for <1 year, 10 for between 1 and 4 years, 11 for between 5 and 9 years, and 1 for >10 years. Five patients who developed malignancy were receiving azathioprine for

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

Azathioprine (years of treatment)	n	Died No (%)	Lost to follow up No (%)	Malignancy No (%)
<1	38	5 (13)	0	0
1-4	55	10 (18)	2 (4)	5 (9)
5-9	40	11 (28)	0	3 (8)
≥10	15	1 (7)	0	0

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. In rheumatoid arthritis and in Sjögren's syndrome, however, it has been linked with lymphoma development.^{1 3 4}

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

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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,³⁻⁵ lumbar spine, and the total body.⁵ 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 involvement⁶: 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.⁷ 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 was not significantly different in patients with normal or altered indices of inflammation and in patients with absence or presence of specific autoantibodies. 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.⁵ Many authors

Table 1 Bone mineral density (g/cm²) in women with SSc categorised according to the extent of disease

	Cutaneous disease Mean (SD)			Internal organs affected Mean (SD)	
	Limited (n = 15)	Intermediate (n = 14)	Diffuse (n = 18)	Absent (n = 21)	Present (n = 26)
Total body	1.104 (0.088)	1.085 (0.089)	1.021* (0.077)	1.099 (0.084)	1.024* (0.070)
Lumbar spine	1.038 (0.161)	1.025 (0.141)	0.945* (0.133)	1.032 (0.139)	0.950* (0.144)
Femur neck	0.831 (0.112)	0.886 (0.119)	0.787** (0.102)	0.881 (0.139)	0.790* (0.148)
Os calcis	89 (13.7)	87 (13.7)	63* (10.9)	88 (12.5)	65* (11.2)

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

suggest that the extent of skin involvement is directly related to the extent of visceral involvement and to the severity of the disease.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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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.¹ 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 completely.

I am not persuaded that the patient in question had GCA.

Firstly, the temporal artery biopsy was negative. Definitive criteria for the entity of so-called biopsy negative GCA are lacking, and, in my opinion, this concept remains a problematic one. Negative temporal artery (TA) biopsies do occur in certain subsets of GCA—for example, upwards of 50% of patients with so-called large artery involvement have such negative biopsies²—but the extent to which TA biopsies are negative in bona fide cases of cranial arteritis in GCA is unclear. Two recent papers have suggested that in fact a unilateral TA biopsy negative for arteritis markedly reduces the probability of the diagnosis of GCA, because the yield of a positive contralateral biopsy is no more than 1–3%.^{3,4}

The issue of what constitutes a flare in GCA (and PMR) is also problematic. It has been my experience over the years that many cases of alleged flares of both conditions involve little more than asymptomatic rises in the acute phase reactants, and that the pursuit of such rises with increased doses of steroids not uncommonly results in sundry untoward complications—notably, steroid induced osteoporosis and associated fractures.

The patient under discussion is a case in point. The acute phase reactants were raised coincident with the occurrence of a TIA, but it is unlikely that this latter episode was caused by GCA. Though GCA is occasionally complicated by stroke, such an event nearly always involves the territory of the vertebral-basilar circulation, and rarely occurs in the distribution of the internal carotid artery. The explanation for this fact may result from the specific exclusion of the intracranial arteries from involvement by GCA, possibly because these arteries lack an internal elastic lamina, which plays a pivotal part in the pathogenesis of GCA. The internal elastic lamina is said to be maintained for a few millimetres after the vertebral arteries pierce

the dura, thus accounting for the strokes referable to the vertebral-basilar circulation.⁵ The patient described by Tan *et al* had left arm weakness, almost surely attributable to ischaemia of the middle cerebral artery, thus effectively ruling out GCA as the cause for the TIA.

I therefore submit that this patient did not have “resistant giant cell arteritis”; rather, he represents a case of the successful treatment by tumour necrosis factor α (TNF α) blockade of symptoms and signs referable to PMR.

One final caveat: although further study may show that TNF α blockade does successfully reduce 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,⁶ 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 TNF α blockade.

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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, reported visual 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, as in this case, 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 Bardin¹ makes an excellent point. We could benefit from the hypouricaemic 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 arterial disease or hyperlipidaemia.^{2–4} However, the mechanisms involved are not clear cut; we speculate that atorvastatin can increase renal blood flow and decrease serum creatinine levels.^{2–4} 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 = 5963) or without (n = 14 573) diabetes.⁵ This effect on GFR would almost certainly influence urate excretion. These statin mediated effects are relevant because, as Professor Bardin¹ points out, patients with hyperuricaemia may also be dyslipidaemic.

Closer 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.^{6,7} Azapropazone (not used as a first line option) has been shown to lower serum urate levels.^{7,8} Indometacin may have uricosuric properties.⁷ Tiaprofenic acid

is another NSAID with hypouricaemic effect.⁹

Aspirin has a bimodal effect on the renal handling of uric acid. High doses (>3 g/day) are uricosuric, while lower doses (1–2 g/day) cause urate retention.¹⁰ 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.¹⁰

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.

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NOTIFICATION AND CORRECTION

Corrections printed in the journal also appear on the *Annals* website www.annrheumdis.com and are linked to the original publication

Intra-articular rheumatoid nodules and triggering of the knee joint (Tak-Diamant Z, Hoening van Duyvenbode FJ, Eulderink F, Janssen M. *Ann Rheum Dis* 1992;**51**:533–5.)

The name of the first author of this paper has changed from Tak-Diamant Z to Diamant Z.

Does long term treatment with azathioprine predispose to malignancy and death in patients with systemic lupus erythematosus? (Nero P, Rahman A, Isenberg DA. *Ann Rheum Dis* 2004;**63**:325–6.)

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We regret that the references for this letter were omitted. They are given below.

1. Hazleman B. Incidence of neoplasms in patients with rheumatoid arthritis exposed to different treatment regimens. *Am J Med* 1985;**78**(suppl 1A):39–43.
2. Moll JMH. Drug therapy (3): “specific” drugs. In: *Management of rheumatic disorders*. 1st ed. London: Chapman and Hall: 1983:169–212.
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4. Sutcliffe N, Smith C, Speight PM, Isenberg DA. Mucosa-associated lymphoid tissue lymphomas in two patients with rheumatoid arthritis on second-line agents, and secondary Sjögren syndrome. *Rheumatology (Oxford)* 2000;**39**:185–8.

NOTICE

8th EULAR Postgraduate Course in Rheumatology

28 November–3 December 2004; Prague, Czech Republic

The course will cover clinical aspects of rheumatic disease concentrating on outcome, assessment, and evidence based management and will include the scientific basis of rheumatology. The course is aimed at junior rheumatologists at the end of their training but is open to all rheumatologists.

The registration fee of €600 will include tuition, accommodation for seven nights and all meals.

The electronic registration system will open on 1 April 2004 on the EULAR website www.eular.org

EULAR will consider granting bursaries to young rheumatologists from countries where there is a real educational need. More information will be available on the EULAR website from 1 April 2004.

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Email: secretariat@eular.org
Website: www.eular.org

FORTHCOMING EVENTS

International Congress on SLE and Related Conditions

9–13 May 2004; New York, New York, USA
Contact: The Oakley Group, 2014 Broadway, Suite 250, Nashville, Tennessee 37203, USA
Tel: +1 615 322 2785
Fax: +1 615 322 2784
Email: Lupus2004@theoakleygroup.com
Website: <http://www.lupus2004.org>

IOF World Congress on Osteoporosis

14–18 May 2004; Rio de Janeiro, Brazil
IOF awards are available for scientists:
IOF Claus Christiansen Research Fellowship: 45 000
IOF 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–5 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
Tel: 00 1 416 480 4833
Fax: 00 1 416 480 6055
Email: shirley.fitzgerald@sw.ca

8th EULAR Sonography Course

7–9 June 2004; Berlin, Germany
Organising Committee: Marina Backhaus, Wolfgang Schmidt
Contact: Congress Organisation: Gedel Congress Service
Tel: +49-30-22488390
Fax: +49-30-22488389
Email: gedel.cm@t-online.de
Website: www.eular.org

First European Course: Capillaroscopy and Rheumatic Diseases

10–12 September 2004; Genova, Italy
Contact: Scientific Secretariat: Professor Maurizio Cutolo, Division of Rheumatology, DIMI, University of Genova, Italy
Email: mcutolo@unige.it
Organising Secretariat: Michela Civelli, EDRA spa, Viale Monza, 133 – 20125, Milan, Italy
Tel: +39 02 281 72300
Fax: +39 02 281 72399
Email: edracongressi@dsmedigroup.com

XIth International Conference on Behçet's Disease

27–31 October 2004; Antalya, Turkey
Contact: Congress Secretariat, Figur Congress and Organization Services Ltd. STI, Ayazmaderesi Cad. Karadut Sok. No: 7 80888 Dikilitas, Istanbul, Turkey
Tel: +90 (0212) 258 6020
Fax: +90 (0212) 258 6078
Email: behcet2004@figur.net
Website: www.behcet2004.org