LETTERS

document of the Dutch Society for Rheumatology

P P Geusens, R N J de Nijs, W F Lems, R F J M Laan, A Struijs, T P van Staa, J W J Bijlsma

Ann Rheum Dis 2004;**63**:324–325. doi: 10.1136/ard.2003.008060

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 <-1.5[7] 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.

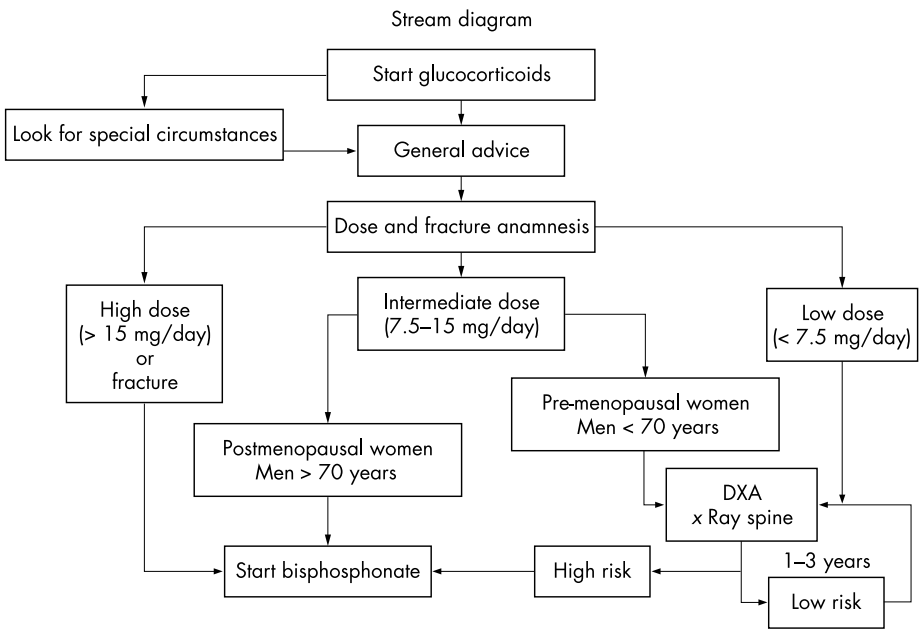

Figure 1 Stream diagram for osteoporosis prevention in GIOP.

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.

Authors' affiliations
P P Geusens, Academisch Ziekenhuis Maastricht, The Netherlands and Limburgs Universitair Centrum, Diepenbeek, Belgium
R N J de Nijs, J W J Bijlsma, Universitair Medisch Centrum Utrecht, The Netherlands
W F Lems, Vrije Universiteit Medisch Centrum en Slotervaartziekenhuis, Amsterdam, The Netherlands
R F J M Laan, Academisch Ziekenhuis Nijmegen, The Netherlands
A Struijs, Erasmus Medical Centre Rotterdam, The Netherlands
T P van Staa, Procter and Gamble, UK

Correspondence to: Professor P Geusens, Department of Rheumatology University Hospital Maastricht, 6202 AZ Maastricht, The Netherlands; piet.geusens@ping.be

Accepted 19 May 2003

REFERENCES

1 **Haugeberg G**, Orstavik RE, Uhlig T, Falch JA, Halse JI, Kvien TK. Clinical decision rules in rheumatoid arthritis: do they identify patients at high risk for osteoporosis? Testing clinical criteria in a population based cohort of patients with rheumatoid arthritis recruited from the Oslo Rheumatoid Arthritis Register. *Ann Rheum Dis* 2002;**61**:1085–9.
2 Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. American College of Rheumatology Task Force on Osteoporosis Guidelines. *Arthritis Rheum* 1996;**39**:1791–801.
3 Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. *Arthritis Rheum* 2001;**44**:1496–503.
4 **de Nijs RN**, Jacobs JW, Bijlsma JW, Lems WF, Laan RF, Houben HH, *et al*. Prevalence of vertebral deformities and symptomatic vertebral fractures in corticosteroid treated patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2001;**40**:1375–83.
5 **Nijs RNJ de**, Lems WF, Laan RFJM, Struijs A, Staa TP van, Geusens P, *et al*. Ronde tafelbijeenkomst: preventie en behandeling van glucocorticosteroïd geïnduceerde osteoporose. *Ned Tijdschr voor Reumatologie* 2002;**1**:12–19.
6 **Pols HA**, Wittenberg J. CBO guideline 'Osteoporosis' (second revision). *Ned Tijdschr Geneeskd* 2002;**146**:1359–63.
7 **Eastell R**, Reid DM, Compston J, Cooper C, Fogelman I, Francis RM, *et al*. A UK consensus group on management of glucocorticoid-induced osteoporosis: an update. *J Intern Med* 1998;**244**:271–92.
8 **van Staa TP**, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Oral corticosteroids and fracture risk. *J Bone Miner Res* 2000;**15**:993–1000.
9 **van Everdingen AA**, Jacobs JW, Siewertsz Van Reesema DR, Bijlsma JW. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. *Ann Intern Med* 2002;**136**:1–12.
10 **Nevitt MC**, Ettinger B, Black DM, Stone K, Jamal SA, Ensrud K, *et al*. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. *Ann Intern Med* 1998;**128**:793–800.
11 **Black DM**, Arden NK, Palermo L, Pearson J, Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. *J Bone Miner Res* 1999;**14**:821–8.
12 **Gough AK**, Lilley J, Eyre S, Holder RL, Emery P. Generalised bone loss in patients with early rheumatoid arthritis. *Lancet* 1994;**344**:23–7.
13 **Haugeberg G**, Uhlig T, Falch JA, Halse JI, Kvien TK. Reduced bone mineral density in male rheumatoid arthritis patients: frequencies and associations with demographic and disease variables in ninety-four patients in the Oslo County Rheumatoid Arthritis Register. *Arthritis Rheum* 2000;**43**:2776–84.

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

P Nero, A Rahman, D A Isenberg

Ann Rheum Dis 2004;**63**:325–326. doi: 10.1136/ard.2002.005371

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