

PostScript

MATTERS ARISING

Treatment of shoulder pain

Hay and colleagues concluded, in their extended report of a trial of physiotherapy and injection for unilateral shoulder pain that physiotherapy and local steroid injection are of similar effectiveness.¹ They suggest that "The high overall success rates... argue against the need for further exploratory trials in this condition". I disagree. A large number of studies of shoulder pain have been bedevilled by diagnostic criteria that are not precise,² and this study must unfortunately join the others.

Unilateral shoulder pain has a number of different causes. The study by Hay excludes a few specific conditions—in particular, a ruptured rotator cuff, but must by definition include a heterogeneous group of problems that are in fact quite discrete. These include frozen shoulder (adhesive capsulitis), rotator cuff injuries without full rupture, subacromial joint arthritis (sometimes known as subacromial bursitis), bicipital tendinitis, acromioclavicular joint disease, and subdeltoid bursitis. It is barely credible to imagine that several of these could be successfully treated by a steroid injection into the subacromial joint. In particular, the subacromial joint does not communicate with the glenohumeral joint unless the rotator cuff is ruptured, so frozen shoulder cannot be treated with a subacromial injection. Thus any study of shoulder pain must separate the different causes into different groups. Others have done this and shown that the relative benefits of physiotherapy and injection may be different.³

Furthermore, it must be clear that any clinicians contributing to a trial are working to the same diagnostic criteria. Even experienced consultant rheumatologists cannot agree on exact diagnoses, as I and colleagues have shown previously,⁴ and we concluded "...recruitment of patients for studies of the treatment of shoulder lesions requires care to avoid selection of a heterogeneous group". Given the variability of rheumatology training and experience in general practice it seems unlikely that diagnostic precision will be sufficient in that setting,

Rapid response

If you have a burning desire to respond to a paper published in the *Annals of the Rheumatic Diseases*, why not make use of our "rapid response" option?

Log on to our website (www.annrheumdis.com), find the paper that interests you, and send your response via email by clicking on the "eLetters" option in the box at the top right hand corner.

Providing it isn't libellous or obscene, it will be posted within seven days. You can retrieve it by clicking on "read eLetters" on our homepage.

The editor will decide as before whether also to publish it in a future paper issue.

and Hay's study does not conform to our recommendation.

For these reasons, far from suggesting that no further research is needed, this study underlines the need for clear and exact diagnostic criteria and further treatment trials for each of the specific causes of unilateral shoulder pain. Partly because clinical diagnosis may be difficult the use of magnetic resonance imaging scanning to define pathology may be an essential part of the investigation before treatment; I have certainly encountered many patients where a clear clinical picture is belied by a scan, particularly in the identification of rotator cuff pathology.

My own local audit of about 800 referrals of patients with shoulder pain suggested that some 40% had a frozen shoulder, with another 40% having abnormality in the rotator cuff/subacromial joint mechanism. Thus one could argue that a pair of steroid injections, one into the glenohumeral joint and one into the subacromial joint, might be expected to benefit about 80% of patients. However, such an approach, while practical, will not resolve in a scientific way the continuing uncertainty over the management of shoulder pain.

A N Bamji

Queen Mary's Hospital Froggnal Avenue, Sidcup, UK

Correspondence to: Dr A N Bamji; andrewbamji@lineone.net

References

- 1 Hay EM, Thomas E, Paterson SM, Dziedzic K, Croft PR. A pragmatic randomised controlled trial of local corticosteroid injection and physiotherapy for the treatment of new episodes of unilateral shoulder pain in primary care. *Ann Rheum Dis* 2003;62:394-9.
- 2 Bamji A. Lack of concordance between rheumatologists may render multicentre studies invalid. *BMJ* 1998;316:1676.
- 3 Ritzmann P. "Frozen shoulder": intraarticular corticosteroids lead to faster pain relief than physiotherapy. *Schweiz Rundsch Med Prax* 1999 Aug 19;88:1369-70.
- 4 Bamji AN, Erhardt CC, Price TR, Williams PL. The painful shoulder: can consultants agree? *Br J Rheumatol* 1996;35:1172-4.

Author's reply

We agree with Bamji that, although a number of ways of classifying shoulder problems have been proposed, none have been shown to be valid or reliable. In our large primary care trial¹ we adopted the "red flag" approach and are clear about its limitations in the paper. Although our trial was pragmatic, it examined a clearly stated question—"in patients presenting to general practitioners with a new episode of unilateral shoulder pain, and in whom specific "red flag" problems have been excluded, is a subacromial injection or a course of physiotherapy the best first choice?".

Essentially, we were comparing two treatments commonly used by general practitioners. We were not investigating the relative merits of different types of injection, or indeed which components of the physiotherapy package had specific benefits. These

are different questions, important in their own right, but not the ones we chose to answer in this particular study.

E M Hay

Staffordshire Rheumatology Centre, The Haywood, Burslem, Stoke-on-Trent, Staffordshire ST6 7AG, UK

Correspondence to: Dr E M Hay; e.m.hay@keele.ac.uk

Reference

- 1 Hay EM, Thomas E, Paterson SM, Dziedzic K, Croft PR. A pragmatic randomised controlled trial of local corticosteroid injection and physiotherapy for the treatment of new episodes of unilateral shoulder pain in primary care. *Ann Rheum Dis* 2003;62:394-9.

Do etanercept-naive patients with rheumatoid arthritis respond better to infliximab than patients for whom etanercept has failed?

We read with interest the article by van Vollenhoven *et al.*¹ In short, they report on 31 patients with rheumatoid arthritis (RA), 18 of whom used etanercept (ETA) first and then switched to infliximab (IFX) in most part because of inefficacy, and 13 patients who used IFX first and changed to ETA mostly owing to adverse events. They suggested using the other tumour necrosis factor (TNF) inhibitor when one of them fails. Although, in general, agreeing with their findings, we would like to present our experience which is somewhat different from theirs and to discuss the possible reasons for this.

We set up an IFX registry at the Hospital for Special Surgery in February 2000, with the start of IFX infusions. The registry collected prospective data on all the patients with RA who started treatment with IFX, and followed up them every 2 months until May 2001. All patients completed questionnaires about their RA history, treatment, and functional disability (modified Health Assessment Questionnaire (mHAQ)) at baseline and every 2 months thereafter. A 42 joint count for tender and swollen joints was performed at each visit. Patients were telephoned 3-5 days after infusions and asked about reactions while at home.

The availability of ETA before the approval of IFX and the fact that use of ETA did not require concomitant methotrexate has resulted in the treatment of more patients with RA with ETA before trying IFX. However, after failure of ETA, several patients changed treatment to IFX. We compared response to treatment, adverse events, and discontinuation rates between patients for whom ETA had failed before IFX treatment (ETA-F) and patients who had not used ETA before—that is, etanercept-naive (ETA-N).

Eighty eight patients were treated with IFX between February 2000 and May 2001 (77 women, mean (SD) age 61 (12.1) years, mean (SD) RA duration 13.4 (9.8) years, failed DMARDs 2). In 37 (42%) patients ETA had failed before IFX was introduced. There was no difference in age, disease duration, and number of failed DMARDs between ETA-F and ETA-N patients. Sixteen ETA-F and 10

ETA-N patients were excluded from the analysis owing to an insufficient number of data points. mHAQ, pain scores, and morning stiffness improved significantly in ETA-N patients, whereas no improvement was noted among the group of ETA-F patients, in the first year after they were receiving IFX. Six ETA-F and seven ETA-N patients discontinued treatment after 4 and 5.7 months, respectively. No significant difference in the number of adverse events was found between ETA-F and ETA-N patients.

We also analysed the functional change and rate of adverse events among patients with RA treated with IFX for those receiving concomitant methotrexate (MTX-R) and those not (MTX-NR). Baseline age and disease duration of MTX-R and MTX-NR patients were similar. IFX treatment was discontinued in 15/42 (36%) MTX-R subjects and 12/46 (26%) MTX-NR subjects. After an average of 6.7 months' follow up 40/61 subjects experienced 96 adverse events (AEs) over a total of 648 infusions; 16/27 (59%) MTX-NR subjects had 46 AEs, compared with 24/34 (71%) MTX-R subjects who had 50 AEs ($p=0.51$). Most of these AEs were minor and none resulted in IFX discontinuation. There was no difference in mHAQ, pain score, swollen and tender joint counts between the MTX-R and MTX-NR groups after 6 months of treatment.

Our clinical experience demonstrates a better clinical response to IFX among ETA naive patients. Based on our data, we would suggest that if ETA fails there might not be a substantial benefit in trying IFX later on. Also, we did not note any difference in the rates of discontinuation or AEs, or response to treatment between MTX-R and MTX-NR patients beyond 6 months of IFX treatment.

We are limited by the number of our patients, just as van Vollenhoven *et al* were. We also do not have data for patients who switched from IFX to ETA because of the shortage of ETA at the time of our study. These results may reflect a population of refractory patients with RA who have more severe disease (patients for whom multiple DMARDs had failed) and are generally difficult to manage, or who are non-anti-TNF responders. Analysis of ETA-F patients who respond to IFX may show a subgroup who will benefit from different anti-TNF formulations. Given the cost of anti-TNF drugs, larger groups should be studied to determine the characteristics of patients who might benefit from a trial of another anti-TNF agent when one has already failed.

Y Yazici

Brooklyn Heights Arthritis Associates, Long Island College Hospital, New York, USA

D Erkan

Hospital for Special Surgery, New York, USA

Correspondence to: Dr Y Yazici; yaziciy@hss.edu

Reference

- 1 van Vollenhoven R, Harju A, Brannemark, Klareskog L. Treatment with infliximab (Remicade) when etanercept (Enbrel) has failed or vice versa: data from the STURE registry showing that switching tumour necrosis factor α blockers can make sense. *Ann Rheum Dis* 2003;**62**:1195–8.

Author's reply

We genuinely appreciate Drs Yazici and Erkan's interest in our paper.¹ The observa-

tions they report based on their own infliximab registry are very interesting indeed. In that registry, patients for whom etanercept treatment had previously failed responded less well to treatment with infliximab than etanercept-naive patients. This is not, in itself, a contradiction to our published report, the gist of which was that patients can have meaningful and significant responses to infliximab even if they failed to respond to etanercept—without making a direct comparison with the results seen in etanercept naive patients. However, it would be of interest to know more details about Drs Yazici and Erkan's patient group.

For instance, the fact that 15 of 21 patients who were said to be "non-responders" continued treatment with infliximab suggests that some measure of improvement was none the less achieved. We have previously published data showing that a sharp distinction between "responders" and "non-responders" is an artefact and that responses in fact are normally distributed.²

Yazici and Erkan also suggest that infliximab with or without concomitant methotrexate provides similar clinical results. In our own database only a few patients received infliximab without concomitant methotrexate so we cannot provide any data bearing directly on this issue. We do note, however, that the important radiological benefits of treatment with infliximab have only been documented in patients receiving background methotrexate.³ Thus, we continue to favour this combination when possible.

R F van Vollenhoven

Department of Rheumatology, Karolinska Hospital, D2-1, 17176 Stockholm, Sweden

Correspondence to: Associate Professor R F van Vollenhoven; ronald.vanvollenhoven@ks.se

References

- 1 van Vollenhoven R, Harju A, Brannemark S, Klareskog L. Treatment with infliximab (Remicade) when etanercept (Enbrel) has failed or vice versa: data from the STURE registry showing that switching tumour necrosis factor α blockers can make sense. *Ann Rheum Dis* 2003;**62**:1195–8.
- 2 van Vollenhoven RF, Klareskog L. Clinical responses to tumor necrosis factor α antagonists do not show a bimodal distribution. Data from the Stockholm tumor necrosis factor α registry. *Arthritis Rheum* 2003;**48**:1500–3.
- 3 Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, *et al*. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000;**343**:1594–602.

Seronegative antiphospholipid syndrome

I agree with Hughes and Khamashta that the use of the term "seronegative antiphospholipid syndrome (APS)" is useful in clinical practice.¹ However, the analogy with seronegative rheumatoid arthritis and antinuclear antibody (ANA) negative lupus is not correct. The current criteria for the classification of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) allow the diagnosis of RA or SLE to be made even if the rheumatoid factor or the ANA is negative, and therefore, seronegative RA and ANA negative SLE are embraced within the classification criteria and as such are not separate entities.^{2–4}

In the case of APS (Hughes' syndrome), the current preliminary classification criteria do not allow a diagnosis of APS to be made in the absence of at least two positive tests for either anticardiolipin antibodies or lupus anticoagulant at least 6 weeks apart.⁵ A revised international consensus statement on classification criteria for APS (Hughes' syndrome) is required to accommodate the seronegative clinical entity.

A S M Jawad

Department of Rheumatology, The Royal London Hospital, Bancroft Road, London E1 4DG, UK

Correspondence to: Dr A S M Jawad, alismjawad1@hotmail.com

References

- 1 Hughes GRV, Khamashta M. Seronegative antiphospholipid syndrome. *Ann Rheum Dis* 2003;**62**:1127.
- 2 Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315–24.
- 3 Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus (SLE). *Arthritis Rheum* 1997;**40**:1725.
- 4 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. *Arthritis Rheum* 1997;**40**:1725.
- 5 Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC *et al*. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome. Report of an International Workshop. *Arthritis Rheum* 1999;**42**:1309–1311.

Authors' reply

We take Dr Jawad's points and agree fully. We also believe that classification criteria are too often wrongly used in diagnosis. Our aim in writing the leader¹ was to highlight what we believe to be a not uncommon diagnostic situation—the patient with many of the features of the syndrome in whom tests remain stubbornly negative.

G Hughes, M Khamashta

Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, London SE1 7EH, UK

Correspondence to: Dr M A Khamashta, munther.khamashta@kcl.ac.uk

Reference

- 1 Hughes GRV, Khamashta M. Seronegative antiphospholipid syndrome. *Ann Rheum Dis* 2003;**62**:1127.

Ibandronate and prevention of postmenopausal osteoporosis

Stakkestad *et al* reported a clinical trial where intravenous (IV) ibandronate injections, given every 3 months during 1 year, produced a dose dependent gain in mean (SD) lumbar spine bone mineral density (BMD) compared with placebo in prevention of bone loss in postmenopausal women.¹ The treatment was then proposed as an alternative to oral bisphosphonates and hormonal therapy in preventing postmenopausal osteoporosis.

The primary outcome was the relative change from baseline in lumbar BMD after 2 years of treatment tested by analysis of

variance, with treatment group and stratum as independent variables. We found several limitations.

Firstly, the initial study was planned for 2 years, but was stopped at 12 months because of the interesting results of the IV ibandronate pivotal phase III fracture study.² Was it possible to infer that results obtained from a trial on fracture occurrence would apply to the study of BMD?

Secondly, given the limited changes in BMD, it could be suggested that they might be due to random variability in the procedure. The least significant change (LSC) in BMD is the percentage of change that is unlikely to be due to the precision error of the procedure. The LSC is 2.8-fold the precision error of the procedure on a specific device, site of measurement, and number of measurements.³ Precision error was not evaluated in the study. The sample size was calculated with an expectation of a significant change in lumbar spine BMD of 3% compared with placebo after 2 years of treatment. Would a 3% change be clinically relevant according to the variability of the measure?

Thirdly, analysis of variance was used for a dose-response model. Multiple comparisons were performed without using post hoc tests which would have adjusted the nominal threshold. The type I error would have been lower than 0.05.

Keeping these limitations in mind, on a clinical ground, IV ibandronate still needs to prove its efficacy on BMD gain.

M Maravic, P Landais

Hôpital Necker Enfants Malades (APHP), France

Correspondence to: Dr M Maravic, 149 rue de Sèvres Paris Cedex 15, France75743; milka-maravic@noos.fr

References

- 1 **Stakkestad JA**, Benevolenskaya LI, Stepan JJ, Skag A, Nordby A, Oefjord E, *et al*. Intravenous ibandronate injections given every three months: a new option to prevent bone loss in postmenopausal women. *Ann Rheum Dis* 2003;**62**:969–75.
- 2 **Recker RR**, Stakkestad JA, Felsenberg D, Chesnut III CH, Christiansen C, Etinger MP, *et al*. A new treatment paradigm: quarterly injections of ibandronate reduce the risk of fractures in women with postmenopausal osteoporosis (PMO): results of a 3-years trial [abstract]. *Osteoporos Int* 2000;**11**(suppl 2):S209.
- 3 **Gluer CC**. Monitoring skeletal changes by radiological techniques. *J Bone Miner Res* 1999;**14**:1952–62.

Author's reply

On behalf of my fellow authors, I welcome the opportunity to respond to the points raised in the letter by Milka Maravic and Paul Landais. Their letter proposed several limitations of our recently published study, which investigated the efficacy and safety of intermittent intravenous (IV) ibandronate (0.5 mg, 1 mg, and 2 mg) injections in the prevention of postmenopausal osteoporosis.¹

In their first comment, Maravic and Landais question why the suboptimal findings from the IV ibandronate pivotal phase III fracture prevention trial led to our study being stopped prematurely after 1 year. In that trial, 0.5 mg and 1 mg IV ibandronate injections every 3 months failed to reduce vertebral fracture risk significantly, relative to placebo.² The decision to stop our study prematurely was taken by the sponsors,

Hoffmann-La Roche Ltd, because of ethical concerns; it was decided at the time that patients should not continue to receive treatment potentially associated with suboptimal efficacy.

However, upon analysis of the results from the fracture prevention study, it became evident that the suboptimal antifracture efficacy was due to under dosing and that higher doses would probably provide the required gains in bone mineral density (BMD) and decreases in biochemical markers of bone turnover. The proposition that higher doses of ibandronate would produce optimal efficacy is supported by the results from a study that evaluated the dose-response relationship associated with intermittent IV ibandronate injections in postmenopausal women with osteoporosis.³ In that study, a 2 mg dose of ibandronate provided significantly greater BMD increases and suppression of bone resorption markers than the 1 mg dose investigated in the fracture prevention study.

The available results from our study were analysed to enable further evaluation of the dose-response relationship of intermittent IV ibandronate. As reported, although our study was terminated prematurely, sufficient results were collected to allow analysis of data for the first year of the study. These results support those seen previously: intermittent IV ibandronate produced a dose dependent effect on BMD and biochemical markers of bone resorption, with the highest dose producing the greatest efficacy. Owing to the findings from our study, together with those from prior studies, a large non-inferiority trial is continuing to determine whether a higher dose (3 mg every 3 months) or a shorter dosing interval (2 mg every 2 months) of IV ibandronate provides equivalent therapeutic efficacy relative to an oral daily ibandronate regimen, which has proved antifracture efficacy (the Dosing IntraVenous Administration study).

In their second observation on our study, the authors imply that the observed changes in BMD might have been due to the random variability associated with the procedure. However, all the BMD measurements in our study were centrally assessed by Synarc (Ballerup, Denmark), where they were also quality assured. Synarc is a well respected company that employs radiologists who are leading experts in clinical trial radiology. Thus, any variability in the assessment of spinal BMD in our study would have been kept to a minimum and the precision error (PE) associated with the measurements would be unlikely to have exceeded 1%.

Hence, as defined by several authors, including Gluer *et al*,⁴ the percentage of BMD change that is unlikely to be due to the variability (PE) of these measurements (the least significant change) is expected to be about 2.8% (1% multiplied by 2.8). As a result, the sample size calculations used in our study, which were based on an expectation of a significant change in lumbar spine BMD of 3% versus placebo after 2 years of treatment, were justified. Because the 3% change exceeds the 2.8% variability of the measurement procedure, it is considered clinically relevant.

In their third comment, the authors correctly state that analysis of variance was used to investigate the efficacy of the three ibandronate regimens. They go on to advise that because multiple comparisons were performed, adjustments should have been made to ensure the maintenance of the overall type I error. However, as only three tests were performed for the primary end point (the relative effect of treatment on lumbar spine BMD), all of which were highly significant, it was not deemed necessary to apply adjustments.

Additional analyses were conducted to determine the influence of baseline spinal BMD and/or time since menopause on the primary end point. In retrospect, as a number of comparisons were performed when conducting these secondary analyses, we agree with Maravic and Landais that relevant adjustments would be optimal. Thus, we have retrospectively applied a Bonferroni correction, a well recognised test to adjust for multiple comparisons. Despite the highly conservative nature of such statistical adjustments when the number of repeated tests is >5, only two results changed (table 1).

Therefore, reassuringly, the findings observed after applying the Bonferroni correction were similar to those reported in our publication.

In summary, although our randomised, double blind, placebo controlled study was prematurely discontinued, sufficient 1 year data from almost 600 patients were available to allow an adequate assessment of the efficacy of IV ibandronate injections in postmenopausal women without osteoporosis. We found that ibandronate dose dependently prevents postmenopausal bone loss, even when considering the variability associated with measuring BMD, and even when adjusting for multiple, repeated statistical assessments. Of note, the highest dose of ibandronate produced gains in BMD that were comparable to those observed with other therapeutic agents in this setting.

Table 1 Summary of the effect of ibandronate on mean lumbar spine BMD, relative to baseline, after 12 months of treatment (%)

Stratum	Time since menopause (years)	Ibandronate			
		Placebo	0.5 mg	1.0 mg	2.0 mg
T score					
> -1	1-3	-0.0	1.1	1.1	1.8†
≤ -1, ≥ -2.5	1-3	-0.7	0.4	1.9*	2.8*
> -1	>3	-0.4	1.4†	1.9*	1.9*
≤ -1, ≥ -2.5	>3	-0.2	1.4*	2.2*	2.9*

*Difference between active group and placebo was significant (p<0.05), even when a Bonferroni correction was applied; †According to an ANOVA test, the difference between active group and placebo was significant (p<0.05). Significance was not achieved when a Bonferroni correction was applied.

Thus, as stated in the conclusion of our publication, intermittent IV ibandronate injections offer the promise of an effective and convenient alternative to current treatments for the prevention of postmenopausal bone loss.

J A Stakkestad

CECOR AS, Nygårdsveien 6, PO Box 1364 Gard, 5507, Haugesund, Norway

Correspondence to: Dr J A Stakkestad; jacobas@cecor.no

References

- 1 **Stakkestad JA**, Benevolenskaya LI, Stepan JJ, Skag A, Nordby A, Oefjord E, *et al.* Intravenous ibandronate injections given every three months: a new option to prevent bone loss in postmenopausal women. *Ann Rheum Dis* 2003;**62**:969–75.
- 2 **Recker RR**, Stakkestad JA, Felsenberg D, Chesnut III CH, Christiansen C, Ettinger MP, *et al.* A new treatment paradigm: quarterly injections of ibandronate reduce the risk of fractures in women with postmenopausal osteoporosis (PMO): results of a 3-year trial. *Osteoporos Int* 2000;**11**(suppl 2):S209.
- 3 **Adami S**, Delmas P, Felsenberg D, Christiansen C, Robinson J, Coutant K, *et al.* Three-monthly 2 mg intravenous ibandronate bolus injections significantly increase bone mineral density in women with postmenopausal osteoporosis [abstract]. *Osteoporos Int* 2002;**13**(suppl 1):S14.
- 4 **Gluer CC**. Monitoring skeletal changes by radiological techniques. *J Bone Miner Res* 1999;**14**:1952–62.

Atherosclerosis in primary antiphospholipid syndrome

We read with great interest the article by Medina *et al* about atherosclerosis in primary antiphospholipid syndrome (APS).¹ They showed that the intima-media thickness (IMT) of carotid arteries from patients with primary APS was greater than that of age and sex matched controls.

We wish to comment on their methodology and findings. For the ultrasound technique Medina *et al* did not define the area where the measurement of IMT was taken, nor did they specify whether the anterior or posterior carotid wall was measured. The anterior or near wall is prone to reverberation artefact, making placement of the callipers difficult. IMT should be measured at a site away from atheromatous plaques. The figures provided by Medina *et al* show that colour and power Doppler were used to define the lumen of the vessel, but there is no mention of how these were standardised. The gain, pulse repetition frequency, prioritisation of colour versus grey scale, use of contrast agents, angle of insonation, and the velocity of blood flow (systole or diastole) will all affect the position of the border of the colour echo in the image and hence affect the readings taken. Their fig 2B shows that the colour echo does not conform to the “white line” of the intimal-luminal interface. Furthermore, the placement of the measurement callipers in figs 2B and 3B is not correct. Here most workers advise that the image be magnified to facilitate accurate calliper placement. Also, the effect of laminar or plug flow patterns may influence readings. With their technique even IMT readings in their controls are far higher than those reported in the world literature (reviewed by Aminbakhsh and Mancini²).

We would have liked to see the antiphospholipid antibody (aPL) titre of the their patients and how they ranked if entered in their regression model in table 3.

A previous study identified IgG anticardiolipin antibody (aCL) as an independent predictor of carotid IMT, suggesting a possible dose effect of IgG aCL on IMT.³ Therefore aPL titres at the lower end of the medium range (20–80 GPL) may be less atherogenic than those at the higher end of the same range.

To confuse matters further, most of their patients with primary APS had other significant conventional risk factors for atherosclerosis, whether in isolation or combination. The prevalence of hypertension, hyperlipidaemia, and obesity was 36%, 54%, and 25%, respectively, in their cohort with several patients having more than one risk factor.

We question the author’s conclusion of atherosclerosis in primary APS. As it stands, their scanning technique overestimates IMT readings, and other conventional cardiovascular risk factors are overrepresented in their cohort, potentially masking the atherogenic potential of aPL.

P R J Ames, K Sokoll

Academic Department of Rheumatology, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, UK

M Weston

Department of Radiology, St James’s University Hospital, Beckett Street, Leeds LS9 7TF, UK

A Margarita, V Brancaccio

Angiology and Coagulation Units, Cardarelli Hospital, Via A Cardarelli, 80100 Naples, Italy

Correspondence to: Dr P R J Ames, paxmes@aol.com

References

- 1 **Medina G**, Casas D, Jara LJ, Vera-Lastra O, Fuentes M, Barile L, *et al.* Increased carotid artery intima-media thickness may be associated with stroke in primary antiphospholipid syndrome. *Ann Rheum Dis* 2003;**62**:607–10.
- 2 **Aminbakhsh A**, Mancini GB. Carotid intima-media thickness measurements: what defines an abnormality? A systematic review. *Clin Invest Med* 1999;**22**:149–57.
- 3 **Ames PRJ**, Margarita A, Delgado Alves J, Tommasino C, Iannaccone L, Brancaccio V. Anticardiolipin antibody titre and plasma homocysteine level independently predict intima media thickness of carotid arteries in subjects with idiopathic antiphospholipid antibodies. *Lupus* 2002;**11**:208–14.

Authors’ reply

We thank Dr Ames *et al* for their interest in our study and for their comments about our methodology and findings of atherosclerosis in primary antiphospholipid syndrome (APS).¹

We agree about the difficulties of anterior carotid wall measurements. Therefore our intima-media thickness (IMT) measurements were performed on the posterior wall, as is shown in fig 2B. Our patients did not have atheromatous plaques, consequently this artefact did not alter the IMT measurement. The colour and power Doppler ultrasound were standardised in our hospital according to the method of Cantú-Brito *et al.* Briefly, the sensitivity and specificity of the method were 91.3 and 92.7%, respectively.² A composite measure that combined the maximal common carotid artery IMT and maximal internal carotid artery IMT was obtained by averaging

these two measurements after standardisation with subtraction of the mean and division by the standard deviation for the measurement.

Colour Doppler cannot define the “white line”, but this technique does define the intimal-luminal interface. The position of the callipers in fig 2B is correct for IMT measurement, but in fig 3B the callipers are showing the indentations in the lumen vessel.

The carotid artery IMT in our controls was 1.2 (0.44) mm. This value is higher than that reported in other studies but, however, only 7/28 controls had an IMT >1 mm. The mean IMT in these seven controls was 1.65 mm (range 1.1–2). The explanation of these results is that the controls also had other cardiovascular risk factors and they were hospital workers. In other studies performed in Mexico, IMT was detected in more than 60% of people from the general population.³

In our regression model we did not include the titres of anticardiolipin antibodies, because we did not determine them simultaneously with the carotid artery IMT study. We have only historical data of antiphospholipid antibodies. We are currently analysing the association of antiphospholipid antibodies and other new risk factors with carotid artery IMT.

In relation to conventional risk factors for atherosclerosis, we agree that these are confusing variables, but the logistic regression analysis controlled for these factors. Certainly, it is very difficult to have patients and controls who do not have traditional risk factors for atherosclerosis.

In view of all the above mentioned information, we think that our patients with primary APS had a significantly greater IMT of the carotid arteries than the controls.

The results are not overestimated because all ultrasound scanning was performed under similar conditions in both groups, by a single experienced radiologist who was unaware of the clinical information, and using the same sonograph equipment.

L J Jara

Clinical Research Unit, Hospital de Especialidades Centro Médico La Raza, IMSS, México, Universidad Nacional Autónoma de México

G Medina

Internal Medicine Department, Hospital General No 76, IMSS, México

O Vera-Lastra

Internal Medicine Department, Hospital de Especialidades Centro Médico La Raza, IMSS, México

M Fuentes

Imagenology Department, Hospital de Especialidades Centro Médico La Raza, IMSS, México

Correspondence to: Dr L J Jara, luis_jara_quezada@hotmail.com

References

- 1 **Medina G**, Casas D, Jara LJ, Vera-Lastra O, Fuentes M, Barile L, Salas M. Increased carotid artery intima-media thickness may be associated with stroke in primary antiphospholipid syndrome. *Ann Rheum Dis* 2003;**62**:607–10.
- 2 **Cantú-Brito C**, Rodríguez-Saldaña J, Reynoso-Marengo MT, Marmolejo-Henderson R, Barinagarrementeria-Aldatz F. Cardiovascular risk factors and carotid atherosclerosis detected by ultrasonography. *Salud Publica Mex* 1999;**41**:452–9.
- 3 **Rodríguez-Saldaña J**, Cantú-Brito C, Sosa-Espinosa P, Reynoso-Marengo MT, Zuckermann Foullón D, Barinagarrementeria-Aldatz F.

Prevalencia de aterosclerosis carotídea en una población de la ciudad de México. *Arch Inst Cardiol Mex* 1998;68:44–50.

Inflammatory rheumatic disorders

I was interested to read the paper by Guillemin *et al*, where the authors used a detailed questionnaire for a telephone survey of patients to assess rheumatic problems.¹ I have used a similar but somewhat more extensive questionnaire, which was initially designed for doctors such as general practitioners to complete and return through my cyberclinic project.²

In this study we evaluated the feasibility of a rheumatology consultation and advisory service using internet and email. We devised and posted a detailed rheumatology pro forma on our website (www.cyberrheum.org; accessed 26 February 2004) for general practitioners to complete and return on the internet. Two trainee doctors interviewed and completed the pro forma for 207 new patients. Based on this information from the questionnaire alone we were then able to provide provisional diagnoses and management plans, which we compared with those drawn up after a face to face assessment of the same patients in the outpatient clinic. Diagnostic concurrence was noted in the majority of patients (86%), no changes in further investigations, such as radiographs and blood tests, in a sizeable proportion of patients (62%) were necessary, and the majority of patients (74%) required no changes in the treatment plans suggested.

Our results show that it is quite feasible to offer an internet based outpatient consultation and advisory service in rheumatology and possibly other disciplines. Perhaps it is more practical in rheumatology because most of the diagnostic clues lie in a detailed history taken from the patients (as in the patient questionnaire we devised), only then aided by clinical examination and laboratory tests.

To our knowledge this was the first and only internet based service available to general practitioners. This, when established, can enable centres to streamline referral processes and provide early diagnosis and management plans for patients, even before their first appointment, which therefore works as a review appointment (as all the results and details of the patients are available when first attending the clinic). As a result we can cut the consultation time in the clinic to half the usual time required, a consequence of which is that we can see more new patients and perhaps also see more review patients.

We noted that general practitioners were finding it difficult to complete the pro forma on the website with the patients. Therefore, subsequently we devised a patient completed questionnaire, available on the same website, so that patients could complete this pro forma at the GP surgery with the help of an assistant such as a nurse. This facilitates referral and reduces demand on general practitioners' time. We have been able to devise a separate questionnaire,³ again posted on our website, to facilitate referrals relating to osteoporosis services, and reduce our response time to management plans.

We are therefore not surprised that the authors found such a patient questionnaire helpful in telephone surveys. Compared with telephone consultation in this manner, an internet based questionnaire format would

appear to be more convenient and less time consuming. Patients can take their own time in a relaxed manner to do the same. Furthermore, two people are not tied down at the same time—that is, patients can complete and return the questionnaire when convenient, and the researchers or the clinicians can assess such questionnaires at leisure or when convenient. Admittedly, more patients have access to telephone than internet and email, and many do not yet know how to use the latter. Hence, in recent years we have provided “hands-on” training and instructions with a number of road shows⁴ for our patients to keep abreast with new information technology and to increase “equity” and access for our patients in these days of “modernisation” in the health services.

B Pal

South Manchester University Hospital, UK

Correspondence to: Dr B Pal, badal.pal@snuht.nwest.nhs.uk

References

- 1 Guillemin F, Saraux A, Fardellone P, Guggenbuhl P, Behier J-M, Coste J, *et al*. Detection of cases of inflammatory rheumatic disorders: performance of a telephone questionnaire designed for use by patient interviewers. *Ann Rheum Dis* 2003;62:957–63.
- 2 Pal B, Laing H, Estrach C. A cyberclinic in rheumatology. *J R Coll Physicians Lond* 1999;33:400–1.
- 3 Pal B. Cyber/virtual clinic in osteoporosis. A questionnaire base of feasibility study towards a rapid consultation and advisory service. *Ann Rheum Dis* 1999;58(suppl 1):abstr 1010:241.
- 4 Pal B. Internet helps communication between doctors and patients. *BMJ* 200;320:59.

Authors' reply

We appreciate Dr Pal's presentation of a rheumatology consultation and advisory service posted on a website for use by general practitioners, further completed with patient's targeted online questionnaire to facilitate referral processes and care management and reduce demand on general practitioners' time.

Although this is certainly of interest for the consultation and care of patients, a prevalence survey cannot rely on such technology. This is not only because people have more access to telephone than internet and email but also, above all, because people in the general population, the target of such a survey, including people with and without disease, will not spontaneously answer an unexpected questionnaire without a minimum of information and invitation. There would be a severe risk of underestimating the denominator and thus biasing the prevalence.

F Guillemin, A Saraux, P Guggenbuhl, J-M Behier

Ecole de Santé Publique, Faculté de Médecine, BP 184, Nancy, France

Correspondence to: Professor F Guillemin, francis.guillemin@sante-pub.u-nancy.fr

Reference

- 1 Guillemin F, Saraux A, Fardellone P, Guggenbuhl P, Behier J-M, Coste J, *et al*. Detection of cases of inflammatory rheumatic disorders: performance of a telephone questionnaire designed for use by patient interviewers. *Ann Rheum Dis* 2003;62:957–63.

Mycobacterial knee infection in patients with idiopathic inflammatory myositis

We read with interest the report by Callaghan and Allen about a patient with inflammatory myositis who developed *Mycobacterium malmoense* infection in her right knee.¹ The authors state in their discussion that they reviewed the literature and found no cases of isolated joint infection with this organism. However, in this journal, we have previously reported three patients with inflammatory myositis who developed mycobacterial knee infections, one of which was with *M malmoense*.²

It is interesting to see that another case of infection with this rare organism has been described in a patient with inflammatory myositis. We suggest that it is sensible to ensure that synovial fluid aspirated from joints of patients with autoimmune rheumatic disease receiving long term immunosuppressive drugs is sent specifically for mycobacterial culture. Possibly, some atypical mycobacterial infections are being undiagnosed. Such infections could become more common with the increasing use of biological therapies for autoimmune rheumatic disease.

I Haq

ARC Educational Research Fellow, Academic Centre for Medical Education, Royal Free and University College Medical School, 4th Floor Holborn Union Building, Highgate Hill, London N19 5LW, UK

D Isenberg

Centre for Rheumatology, Division of Medicine, The Middlesex Hospital and University College London, 4th Floor Arthur Stanley House, 40–50 Tottenham Street, London W1T 4NJ, UK

Correspondence to: Dr I Haq; i.haq@acme.ucl.ac.uk

References

- 1 Callaghan R, Allen M. Mycobacterium malmoense infection of the knee. *Ann Rheum Dis* 2003;62:1047–8.
- 2 Haq I, Isenberg DA. Myositis and swollen knees: disease or treatment complication. *Ann Rheum Dis* 2002;61:544–6.

Author's reply

Apologies for not picking up this interesting article in our literature search. Drs Isenberg and Haq are, of course, right. Thank you for letting us know.

R Callaghan

Wallsgrave Hospital, Coventry, UK

Correspondence to: Dr R Callaghan; robcallaghan@doctors.org.uk

Increased risk of cancer in patients with scleroderma: no risk in patients with morphea

In a recent issue of the *Annals* Hill *et al* reported a risk of cancer in patients with (systemic) scleroderma. The authors found an increased risk for all cancers, but the greatest significantly increased relative risk was for lung cancer.¹

Published data do not indicate an increased risk of cancer for patients with localised scleroderma or morphea in general.² But that statement needs a closer look. Although there are no population based studies in this field, there is some evidence that patients with pansclerotic or generalised

morphoea with longstanding ulcerations of skin or scars are at risk for the development of squamous cell carcinoma. In a recent overview we found seven case reports on squamous cell carcinoma in patients with pansclerotic or generalised morphoea.³ The number seems remarkably high because this disease is extremely rare. The observation has not only some impact on follow up but on treatment as well. The use of ultraviolet based treatments like UVA1 or PUVA (psoralen plus UVA) widely used successfully for more severe or widespread forms of morphoea⁴ might further increase the risk of squamous cell carcinoma in these patients.

U Wollina

Department of Dermatology, Hospital Dresden-Friedrichstadt, Friedrichstrasse 41, 01067 Dresden, Germany

Correspondence to: Dr U Wollina;
wollina-uw@khdf.de

References

- Hill CL, Nguyen A-M, Roder D, Roberts-Thomson P. Risk of cancer in patients with scleroderma: a population based cohort study. *Ann Rheum Dis* 2003;**62**:728–31.
- Rosenthal AK, McLaughlin JK, Gridley G, Nyren O. Incidence of cancer among patients with systemic sclerosis. *Cancer* 1995;**76**:910–14.
- Wollina U, Buslau M, Weyers W. Squamous cell carcinoma in pansclerotic morphea of childhood. *Pediatr Dermatol* 2002;**19**:151–4.
- Dutz J. Treatment options for localized scleroderma. *Skin Therapy Lett* 2000;**5**:3–5.

Author's reply

Dr Wollina's observations are of great clinical and research interest. Unfortunately, we excluded patients with localised scleroderma in our study¹ owing to incomplete ascertainment in South Australia. We agree that further investigation of this interesting area is needed, particularly in relation to the influence of treatment. However, epidemiological studies of rare diseases are a challenging area of research.

C L Hill

Rheumatology Unit, The Queen Elizabeth Hospital, Woodville Road, Woodville 5011, South Australia

Correspondence to: Dr C L Hill; catherine.hill@nwhs.sa.gov.au

doi: 10.1136/ard.2003.014829

Reference

- Hill CL, Nguyen A-M, Roder D, Roberts-Thomson P. Risk of cancer in patients with scleroderma: a population based cohort study. *Ann Rheum Dis* 2003;**62**:728–31.

NOTICE

MSc Programme in Clinical Rheumatology

Applications are invited for places on this MSc programme, starting September 2004, which provides an excellent academic basis for those aiming at a career in rheumatology or a related subject. Applicants should be medically qualified and should have had at least 2 years of general medical experience after qualification. Previous experience in

rheumatology is desirable, but not essential. The programme is undertaken part time over 2 years and is now well established, entering its 10th year.

Topics covered will include: basic science, clinical skills, peripheral joint problems, spinal problems, connective tissue disease and vasculitis, and the epidemiology of musculoskeletal diseases. A supervised project, which may be either clinical or laboratory based, is an integral part of the programme. The closing date for applications is 31 May 2004.

Further details can be obtained from Miss Lisa McClair, ARC Epidemiology Unit, Stopford Building, University of Manchester, Oxford Road, Manchester, M13 9PT, UK. Tel: (0) 161 275 5993. Fax: (0) 161 275 5043. Email: Lisa.Mcclair@man.ac.uk

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

EULAR 2004

9–12 June 2004; Berlin, Germany
Contact: EULAR Secretariat
Tel: +41 1 383 96 90
Fax: +41 1 383 98 10
Email: secretariat@eular.org
Website: <http://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

4th International Congress on Autoimmunity

3–7 November, 2004; Budapest, Hungary
Deadline for receipt of abstracts: 20 June 2004
Contact: 4th International Congress on Autoimmunity, Kenes International—Global Congress Organisers and Association Management Services, 17 rue du Cendrier, PO Box 1726, CH-1211 Geneva 1, Switzerland
Tel: +41 22 908 0488
Fax: +41 22 732 2850
Email: autoim04@kenes.com
Website: www.kenes.com/autoim2004

8th EULAR Postgraduate Course in Rheumatology

28 November–3 December 2004; Prague, Czech Republic
Contact: EULAR Secretariat, Witikonstrasse 15, CH 8032 Zurich, Switzerland
Tel: +41 1 383 96 90
Fax: +41 1 383 98 10
Email: secretariat@eular.org
Website: www.eular.org

Osteoarthritis Research Society International

2–5 December 2004; Chicago, USA
Contact: 17 000 Commerce Parkway, Suite C, Mt Laurel, NJ 08054, USA
Email: oarsi@oarsi.org
Tel: +001 856 439 1385
or visit <http://www.oarsi.org>

VIth European Lupus Meeting

3–5 March 2005; Royal College of Physicians, London, UK
Contact: Julia Kermode, Conference organiser of the British Society of Rheumatology
Email: Julia@Rheumatology.org.uk

Future EULAR congresses

8–11 June 2005; EULAR 2005; Vienna, Austria
21–24 June 2006; EULAR 2006; Amsterdam, The Netherlands

Future ACR meeting

16–21 October 2004; 68th Annual Scientific Meeting; San Antonio, Texas