


Authors' reply

View metadata, citation and similar papers at core.ac.uk

brought to you by  CORE

provided by DSpace at VU

during the preparation of our manuscript.

Our study described asymptomatic subjects,¹ a somewhat different group from that in Dr Smith's study²—namely, patients with unexplained knee pain with clinically and arthroscopically normal knee joints. It is fascinating that in his study arthroscopy could not detect moderate inflammation seen in some biopsies. Thus, some synovitis can be present even when examinations and gross arthroscopy are normal. Future studies of patients like ours and those of Smith *et al* would benefit from longer follow up. What was the final cause of the knee pain that led to the need for arthroscopy? Will the cellular pattern be consistent, resolving, or progressive in some patients? Do the infiltrates seen in some "normal subjects" have any prognostic significance?

It appears that our two studies^{1,2} with many similar findings reinforce the point, also noted before by Lindblad and Hedfors,³ that there may be more variability in synovial histology and immunohistochemistry than many may have appreciated.

J A Singh, H R Schumacher

Minneapolis VA Medical Center, Minneapolis, USA

Correspondence to: Dr J A Singh; singh046@umn.edu

References

- 1 Singh JA, Arayssi T, Duray P, Schumacher HR. Immunohistochemistry of normal human knee synovium: a quantitative study. *Ann Rheum Dis* 2004;**63**:785–90.
- 2 Smith MD, Barg E, Weedon H, Papangelis V, Smeets T, Tak PP, *et al*. Microarchitecture and protective mechanisms in synovial tissue from clinically and arthroscopically normal knee joints. *Ann Rheum Dis* 2003;**62**:303–7.
- 3 Lindblad S, Hedfors E. The synovial membrane of healthy individuals—immunohistochemical overlap with synovitis. *Clin Exp Immunol* 1987;**69**:41–7.

Low dose prednisolone for treatment of RA

We read with interest the report of the WOSERACT trial¹ that compared the addition of 7 mg daily prednisolone or placebo to sulfasalazine in early rheumatoid arthritis (RA). A number of important aspects of the trial have been dealt with well: the sample size is adequate; appropriate attention has been paid to confounders; two separate and independent readers scored the radiographs; the 2 year trial was of adequate length; and the completeness of the data is satisfactory. Given these strengths, it is all the more disappointing that the results of the main outcome, radiographic damage, cannot be adequately interpreted as they are reported. Indeed, the validity of these results is open to serious doubt. We feel there is a real possibility of a type II statistical error (missing a true difference between treatment arms). There are two (possibly three) reasons for this.

Firstly, there is an absolute difference between the *x* ray scores of the two readers of about 40 Sharp points. This raises strong doubts over the proficiency of either or both readers. In early RA Sharp scores are typically very low, with most patients scoring 0 and only a few with higher scores. Scores of 80, let alone 159, after one year of RA are

without precedent in the literature, and even the baseline medians of 6 and 8 recorded for

change in *x* ray score was consistent between the two readers²: these data are simply not provided in the report. All we have is an unsatisfactory correlation of absolute scores between readers of 0.8 (whereas in most trials the intraclass correlation coefficient (the recommended and more severe test of reliability between readers) exceeds 0.9), and the comparison between readers of differences between the median start and end scores in the two study groups. Unfortunately, the difference between medians at baseline and end point is not the same as the median change.

Secondly, most trials choose two readers who read either with sequence known or unknown (the jury is still out on which is the preferred method), and report the mean of these two readings. This report has two readers, each of whom uses a different one of these options, and this makes it impossible to pool the results. Also, even with sequence unknown, films should be read as sets (all films belonging to one patient assessed simultaneously), not totally at random. Reading totally at random strongly decreases the signal to noise ratio.³ Which method did the "random" reader apply exactly?

A third concern is about the analysis, although this may only be a question of the way in which the data are presented. Although the authors state that the main outcome measure is the change in radiographic damage, they only report medians and ranges of the absolute scores in the groups. From our reading of the report, we fear the analysis has (statistically) compared the distributions of these absolute scores rather than their changes.

This is an important study, and has the potential to add valuable information to our understanding of the best way to treat RA, but in its present form the radiographic results are more likely to cloud the issues than clarify them. We suggest that the radiographs are made available to be re-read by two new, experienced readers, with either the sequence known or unknown to both. We also suggest that the analysis should present the median, range, etc, of the changes in each group, and the test of the difference between these. (If they have a skewed distribution, then either transformation before parametric analysis or the use of non-parametric methods would be the best way to compare the groups.)

There are other difficulties with the study, although these are less important than the essential concerns noted above. For example, we are baffled by the statement in the introduction that the COBRA combination³ "showed radiological advantage over sulfasalazine alone but the study was not powered to detect differences in *x* ray change". In fact, the differences in *x* ray change were among the key findings of the COBRA study, and have since been shown to increase over time.⁴ So the study was not only adequately powered but also showed an unexpectedly large effect.

The authors diminish the value of the report by inappropriate interpretation of their secondary data, especially on the adverse effects. In the discussion they comment, "While observed toxicity from corticosteroids in terms of hypertension, weight gain, and

osteoporosis could be reduced by active assessment and prompt intervention, there

heart disease remained similar, whereas the use of antihypertensive agents increased in both groups, as did prescription of lipid lowering agents. The use of any treatment for osteoporosis also increased in both groups". In fact there was no difference between the groups and thus there was no observed toxicity from glucocorticoids in their study. Further, the authors make no comment on their observation that (many) more patients in the placebo group than in the glucocorticoid group stopped sulfasalazine treatment owing to side effects.

In relation to weight gain, inappropriate attention to within-group changes leads the authors to conclude that body weight "increased significantly" in the glucocorticoid group (median gain 4 kg), with only a "borderline increase" in the placebo group (median gain 3 kg). Body mass index is handled in the same way. However, the only really relevant comparisons, those between groups, do not even show a trend to significance (all *p* values ≥ 0.10). As with the radiographic findings, the presentation of the table suggests end point results were compared rather than change scores.

Our interpretation of the clinical results contradicts that of the investigators, and we conclude that the effects on symptoms are in line with previous reports of limited and temporary advantages for disease activity, blunting of sulfasalazine toxicity, and extremely limited side effects when appropriate caution is applied. It is not possible to assess adequately the main results on *x* ray progression, which are at variance with several previously published studies,^{3–8} and we urge the authors to allow a second read of the radiographs so that their important dataset can be added to the existing evidence.

J Kirwan

University of Bristol Academic Rheumatology Unit, Bristol Royal Infirmary, Bristol BS2 8HW, UK

M Boers

Department of Clinical Epidemiology and Biostatistics, VU University Medical Centre, Amsterdam, The Netherlands

Correspondence to: Dr J Kirwan; john.kirwan@bristol.ac.uk

References

- 1 Capell HA, Madhok R, Hunter JA, Porter D, Morrison E, Larkin J, *et al*. Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: results of a randomised controlled trial. *Ann Rheum Dis* 2004;**63**:797–803.
- 2 Van der Heijde D, Boonen A, Boers M, Kostense P, van Der Linden S. Reading radiographs in chronological order, in pairs or as single films has important implications for the discriminative power of rheumatoid arthritis clinical trials. *Rheumatology (Oxford)* 1999;**38**:1213–20.
- 3 Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, *et al*. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis [see comments] [published erratum appears in *Lancet* 1998;**351**:220]. *Lancet* 1997;**350**:309–18.
- 4 Landewe RB, Boers M, Verhoeven AC, Westhovens R, van De Laar MA, Markusse HM, *et al*. COBRA combination therapy in patients with early rheumatoid arthritis: long-term

- structural benefits of a brief intervention. *Arthritis Rheum* 2002;**46**:347–56.
- 5 Kirwan JR, Arthritis and Rheumatism Council Low Dose Glucocorticoid Study Group. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. *N Engl J Med* 1995;**333**:142–6.
 - 6 Hickling P, Jacoby RK, Kirwan JR. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. *Br J Rheumatol* 1998;**37**:930–6.
 - 7 Rau R, Wassenberg S, Zeidler H. Low dose prednisolone therapy (LDPT) retards radiographically detectable destruction in early rheumatoid arthritis—preliminary results of a multicenter, randomized, parallel, double blind study. *Z Rheumatol* 2000;**59**(suppl 2):II/90–6.
 - 8 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.

Authors' reply

We agree with John Kirwan and Maarten Boers that the assessment of radiographic damage in the WOSERACT study is of importance.¹ The method of reading radiographs has evolved since this study was planned in 1995.² Because we consider that "the jury is out", on the optimal way to read radiographs in studies the films were read (a) at random by one reader and (b) in sequence by the other reader, and the same conclusion was reached. This strengthens rather than weakens the case for a true result.

The study of Paulus *et al.*,³ in which there was no beneficial effect on radiographic outcome in 197 patients with rheumatoid arthritis (RA), supports the WOSERACT study findings. It was unfortunate that in the Arthritis and Rheumatism Council (ARC) low dose corticosteroid study the two groups were not well matched at the outset, making interpretation of the true effect of prednisolone at 2 years and of the subsequent report difficult.^{4,5}

The COBRA study⁶ used a high initial corticosteroid dose and the effects contributing to prompt disease control were multifactorial. It is similarly not possible to extrapolate from the study of van Everdingen *et al.*,⁷ because they used a protocol of steroid without initial disease modifying antirheumatic drug, which is not a practice supported by current guidelines on RA management.

There was considerable discussion among the WOSERACT investigators about the approach to glucocorticoid side effects. It was decided that management of these would be the responsibility of the individual consultant, who remained unaware of the treatment assignment. For this reason there is likely to be a great deal of background noise. This issue was not a primary end point of our study but information is available from other studies.⁸ We do agree that the blunting of sulfasalazine toxicity in the active group is of interest, although it would be inappropriate to advocate the use of prednisolone for this reason alone.

At a time when multiple treatments are increasingly used in early RA it is vital to be certain what contribution, if any, oral corticosteroids might make. The fact that both the ARC study and ours showed no sustained clinical benefit, makes x ray interpretation all the more important.

Thus we suggest that with John Kirwan and Marten Boers an approach is made to the

ARC (the original sponsors of the 1995 study), or to EULAR, for sufficient funding to allow independent readers and statisticians to evaluate all appropriate datasets. This would allow films from relevant studies to be copied and made available as a central repository for future study. The films from the study of Rau *et al.*⁷ would also be useful for this initiative.

H Capell, J Hunter, R Madhok, E Morrison, J Larkin on behalf of the WOSERACT group
Centre for Rheumatic Diseases, Glasgow, UK

Correspondence to: Dr H A Capell; hilary.capell@northglasgow.scot.nhs.uk

References

- 1 Capell HA, Madhok R, Hunter JA, Porter D, Morrison E, Larkin J, *et al.* Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: results of a randomised controlled trial. *Ann Rheum Dis* 2004;**63**:797–803.
- 2 van der Heijde D, Boonen A, Boers M, Kostense P, van der Linden S. Reading radiographs in chronological order, in pairs or as single films has important implications for the discriminative power of rheumatoid arthritis clinical trials. *Rheumatology (Oxford)* 1999;**38**:1213–20.
- 3 Paulus HE, Di Primeo D, Sanda M, Lynch JM, Schwartz BA, Sharp JT, *et al.* Progression of radiographic joint erosion during low dose corticosteroid treatment of RA. *J Rheumatol* 2000;**27**:1632–7.
- 4 Kirwan JR, Arthritis and Rheumatism Council Low Dose Glucocorticoid Study Group. The effect of glucocorticosteroids on joint destruction in rheumatoid arthritis. *N Engl J Med* 1995;**333**:142–6.
- 5 Hickling P, Jacoby RK, Kirwan JR. Joint destruction after glucocorticosteroids are withdrawn in early rheumatoid arthritis. *Br J Rheumatol* 1998;**37**:930–6.
- 6 Landewe RB, Boers M, Verhoeven AC, Westhovens R, van De Laar MA, Markusse HM, *et al.* COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. *Arthritis Rheum* 2002;**46**:347–56.
- 7 van Everdingen AA, Jacobs JW, Siewertsz Van Reesema DR, Bijlsma JW. Low dose prednisolone 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.
- 8 Fries JF, Williams CA, Ramey D, Bloch DA. The relative toxicity of disease-modifying antirheumatic drugs. *Arthritis Rheum* 1993;**36**:297–306.
- 9 Rau R, Wassenberg S, Zeidler H. Low dose prednisolone therapy (LDPT) retards radiographically detectable destruction in early rheumatoid arthritis – preliminary results of a multicenter, randomized, parallel, double blind study. *Z Rheumatol* 2000;**59**(suppl 2):II/90–6.

FORTHCOMING EVENTS

4th International Congress on Autoimmunity

3–7 November, 2004; Budapest, Hungary
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

ARC Epidemiology Unit Golden Jubilee Symposium

4–5 November 2004; Manchester, UK
Rheumatic disease epidemiology: yesterday, today, and tomorrow
Email: gillian.amroon@man.ac.uk
Website: www.arc.man.ac.uk/anniversary

17th Congres Français de Rhumatologie

15–17 November 2004; Paris, France
Contact: Catherine Reillat
Tel: +33 01 42 50 00 18
Fax: +33 01 42 50 10 68
Email: c.reillat.sfr@wanadoo.fr
Website: www.rhumatologie.asso.fr

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 Kermod, Conference organiser of the British Society of Rheumatology
Email: Julia@Rheumatology.org.uk

International Society for the Study of the Lumbar Spine Instructional Course

27, 28 March 2005; Nairobi, Kenya
Controversies in diagnosis and treatment of lumbar spinal conditions
Contact: Shirley Fitzgerald, 2075 Bayview Avenue, Room MG323, Toronto, Ontario, Canada M4N 3M5
Tel: 416 480 4833
Fax: 416 480 6055
Email: shirley.fitzgerald@sw.ca

BSR Annual Meeting 2005

19–22 April 2005; ICC, Birmingham, UK
Joint meeting with the German Society for Rheumatology
Abstract submission deadline 15 November 2004
Contact: BSR, 41 Eagle Street, London WC1R 4TL
Tel: +44 (0) 20 7242 3313
Fax: +44 (0) 20 7242 3277

EULAR 2005

8–11 June 2005; Vienna, Austria
Contact: EULAR Secretariat
Tel: +41 1 383 96 90
Fax: +41 1 383 98 10
Email: secretariat@eular.org
Website: <http://www.eular.org/eular2005>

Future EULAR congress

21–24 June 2006; EULAR 2006; Amsterdam, The Netherlands