

2) had an incomplete response. Patient 4 stopped infliximab treatment in week 49 for 10 weeks because of a labial herpes infection that was treated with acyclovir. Thereafter tumour necrosis factor blocking therapy was successfully restarted.

At 78 weeks 4/5 patients (patients 1, 3, 4, 5) were in complete remission. One patient (patient 2) who had an incomplete response with a 6 weeks' treatment interval showed complete remission after the interval was shortened to 4 weeks. Patient 1 who received his first infliximab dose at our division 160 weeks ago had been responding so well to the treatment that we stopped giving infliximab after his 16th infusion at the end of week 120. Because of disease exacerbation, treatment had to be restarted 26 weeks later and within a few days (data not shown) the patient regained complete remission.

These data, although only retrospectively obtained, suggest that infliximab is a valuable therapeutic tool for treating refractory PsA. So far, permanent discontinuation of treatment owing to toxicity or inefficiency has only been necessary for one of the nine patients.

One possible reason for the different outcome in the effect of infliximab on PsA in our patients and those of Feletar *et al* might be the severity of the joint disease in Feletar's patients. Fifteen out of 16 of their patients had mutilating arthritis, whereas this form of joint destruction was not present in our group. To clarify this possibility, further studies with larger groups and well defined joint disease are necessary.

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Author's reply

Yazdani-Biuki *et al* were surprised that our data on 16 patients with arthritis treated with infliximab demonstrated only a modest response.¹ They contrast our data with data from nine patients with psoriatic arthritis (PsA) treated with infliximab in their centre. Although they mention nine patients, only seven were treated for more than 52 weeks. They claim that eight of the nine patients demonstrated rapid clinical response, but provide information on only five patients who demonstrated a PsA American College of Rheumatology response, four of whom are

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said to be in complete remission. It is not clear whether the other patients discontinued the drug, in which case their withdrawal rate would be 22%.

This is in contrast with the results of our study, which demonstrated a high toxicity rate, and high level of discontinuation (6/16 or 38%). We had previously suggested that the difference between our study and others might reflect the severity of our patient group. The group treated by Yazdani-Biuki *et al* was demographically somewhat different from our group. There were more men in our study (12/16 v 4/5), they were older (48 v 41), and had longer disease duration (14 v 10.5). However, the same average number of disease modifying antirheumatic drugs had been used in the two groups. Yazdani-Biuki *et al* did not provide information on damage in their patients. Our group included five patients with arthritis mutilans; however, all these patients had evidence of inflammatory arthritis. The other five patients may have had evidence of damage but did not demonstrate arthritis mutilans. Because we have previously shown that the presence of damage predisposes not only to progression of damage but also to early mortality in this patient group, we felt it was important to give these patients the best available treatment.^{2,3}

We agree with Yazdani-Biuki *et al* that the difference between the results of our two studies may be related to the difference in disease severity between the two groups. However, the number of patients is too small to draw valid conclusions. It is important to gain more experience with anti-tumour necrosis factor agents both in randomised clinical trials and clinical observational studies, including a wide range of patients with PsA, so that the true level of response and toxicity can be identified.

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Immunohistochemistry of normal synovium

A recent paper published in the *Annals of the Rheumatic Diseases* by Singh *et al* claimed to be the first report of immunohistochemical features of knee synovium in such a large number of healthy normal subjects.¹ This statement is incorrect and I am surprised that the authors of this paper appear to be unaware of our paper published more than 12 months previously in the same journal.²

We studied 20 normal patients attending a sports medicine clinic with unexplained knee pain who had no evidence of any form of arthritis on history, examination, and laboratory tests and had normal x ray findings and normal knee arthroscopy. Although Singh *et al* may argue about the source of our "normal" subjects, it is noted that several of their subjects were not entirely normal either. We are, at least, in a better position to state that our patients were as close as possible to normal than the study of Singh *et al*, who relied on normal x ray examinations to exclude joint pathology (including early osteoarthritis) and included patients with either a positive rheumatoid factor or a raised erythrocyte sedimentation rate (ESR), neither of which was included in our patient group.

In the two studies the patient group and the variables measured in the synovial membrane were similar, and the conclusions of both studies were also similar. Like the study of Singh *et al*, we found quite a variability in the architecture of the normal synovial membrane, particularly in relation to the thickness of the lining layer and the subintimal cell infiltrate, but we also measured cytokine production, cell adhesion molecule expression, and mediators of osteoclast formation, which were not included in the study of Singh *et al*. We did find evidence of B cells and occasional plasma cells in the normal synovial membranes, unlike Singh *et al*, but these cell populations were quite sparse.

It is, however, very surprising that neither the journal reviewers nor the authors of this paper appeared to be aware of a similar paper published in the same journal before this paper was accepted for publication, and we do dispute the statement of Singh *et al* that they have published the "first report of immunohistochemical features of knee synovium in such a large number of healthy normal subjects".

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Authors' reply

We thank Dr Smith for alerting readers and us to the existence of his excellent paper that came out after our study was done and 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.

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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 the conservative reader are quite high. In contrast with the authors, we cannot be "reassured" by their assertion that "the change in x ray score was consistent between the two readers": 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.² 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 is no room for complacency". However, in their results section they report that, "Low dose aspirin and treatment for ischaemic 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.

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