

ciprofloxacin showed a trend towards improvement.⁶ There were not enough post-chlamydial patients in the trial of Kvien *et al* for a meaningful analysis to be made.

We also question the treatment itself in their trial. A one-time dose of 1000 mg of azithromycin is approved for an acute *Chlamydia* infection; however, the proper dose for persistent infection has not been established. To our knowledge, 1000 mg weekly has never even been studied in vitro as a dose to treat persistent *Chlamydia*. In addition, persistent *Chlamydia* infections intermittently shed infectious elementary bodies, potentially evading weekly pulse antimicrobial treatment. It has also been demonstrated that the chronic treatment of *Chlamydia trachomatis* with azithromycin in vitro caused the *Chlamydia* temporarily to arrest in a persistent viable state.⁷ Lastly, it has not been established if 3 months of a single antimicrobial agent is successful at treating an obligate intracellular organism that exists in the form of a reticulate body. Other obligate intracellular organisms, such as *Mycobacterium tuberculosis*, require 9 months of combination antimicrobial treatment to ensure therapeutic response.

Kvien *et al* implied that their trial, along with previous trials, indicates a lack of efficacy of antibiotics in ReA. The antibiotics studied previously included tetracyclines, ciprofloxacin, and now azithromycin.^{1,5,6} *Chlamydia* has demonstrated in vitro resistance to all of these antibiotics upon chronic administration.^{7,8} Further, ciprofloxacin has been shown to cause tendon based inflammation by potentiating interleukin 1 β stimulated metalloproteinase-3 output in tendons.⁹ Is this then the proper antibiotic to choose in the treatment of an enthesophyte based inflammatory arthritis?

We have recently completed a trial assessing a 9 month course of a combination of doxycycline and rifampin versus doxycycline monotherapy.¹⁰ The results showed a rather dramatic response in the patients who received the combination. The chlamydial resistance that has been documented in vitro, was overcome when a combination of antibiotics were used.⁷ Ours was the first trial to assess a combination of antibiotics in this setting.

Do antibiotics work in ReA, specifically *Chlamydia* induced ReA? In our opinion, this question has not been answered. We believe studies of large groups of patients, with the appropriate antibiotics, in the right dose, used for the proper length of time, need to be conducted before this question can be answered.

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Authors' reply

We thank Carter *et al*¹ for their valuable comments on our paper which reported the results of 3 months' treatment of reactive arthritis (ReA) with azithromycin.² The data from our study definitely did not support prolonged use of antibiotics for the alleviation of ReA, because no trend was found in favour of long term treatment. However, we do not disagree that the data from the study by Carter *et al*,¹ and from other authors,³ may support long term treatment with antibiotics in patients with ReA induced by *Chlamydia trachomatis*.

Such positive findings as have been reported seem to be restricted to this microbiological agent. We note that the study by Carter *et al*¹ was performed in patients with chronic undifferentiated spondyloarthritis without confirmed *Chlamydia* infection, but 9 of 30 patients had either a possible or probable preceding symptomatic *Chlamydia* infection.

We also agree that various arguments can be employed in the selection of the optimal antimicrobial agent in ReA. We chose azithromycin in our study because of its acceptable tolerability profile combined with a broad antimicrobial spectrum, as our study was designed to focus on all patients in whom ReA was a likely diagnosis—not just patients with *Chlamydia* induced ReA. Carter *et al* compared doxycycline 100 mg twice a day with doxycycline 100 mg twice a day + rifampicin 600 mg a day.¹ The latter drug is most widely used for the treatment of tuberculosis. The safety of this combination

should be clarified before recommendations are given for its wider use in ReA or undifferentiated spondyloarthritis.

We would also welcome an adequately powered trial confined to patients with *Chlamydia* induced arthritis, to clarify the efficacy or otherwise of long term treatment with antibiotics in this condition. However, in our opinion, such a trial will be difficult to perform, because of the logistic problems of recruiting large numbers of bacteriologically proven cases early in the course of their disease. For the present, therefore, clinicians must base their treatment on currently available data.

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Is Behçet's syndrome associated with infection?

I read with interest that the pustular skin lesions in Behçet's syndrome (BS) had been thought aseptic, were found to be not sterile, and that the microbiology of these lesions is different from ordinary acne.¹ I would like to report my observation of a patient with refractory pustulosis of Behçet's disease, who fulfilled the international study group criteria, was HLA-Bw51 positive, and had a family history of BS. The patient's skin rash disappeared after a 6 week course of cotrimoxazole (sulfamethoxazole-trimetoprim).

The patient, a 31 year old man had had recurrent oral and genital ulcers since childhood. Inflammatory joint disease developed 4 years ago, affecting shoulders, ankles, and knees, relapsing every 2–3 months. Recurrent knee effusions caused serious knee dysfunction. Skin pustulosis, which was episodic at onset, became persistent and massive during the past 4 years, affecting the body, back, and limbs (fig 1A). A skin vesicle was observed 24–48 hours after taking blood for analysis from the knee at the point of needle entry. Polyarthritis and skin pustulosis became refractory to local, systemic, and intra-articular corticosteroids and colchicine. The pustular lesions thought to be sterile in BS were not cultured. Salazopyrin, methotrexate given orally and parenterally at maximal dose of 25 mg/week, and azathioprine failed to control the knee effusions,



Figure 1 Pustulosis of Behçet's disease localised in the right suprascapular area: (A) before co-trimoxazole treatment; (B) on the 10th day of co-trimoxazole treatment (960 mg twice a day).

shoulder and ankle arthritis, skin rash, and oral ulcers. Invasive knee procedures were planned.

At this point the failed second line treatment was stopped, and we made the decision to start co-trimoxazole treatment. The rationale for this was the anti-inflammatory properties of the drug reported previously² and its effectiveness for some patients with Wegener's granulomatosis³ associated with severe neutrophilic activation,⁴ which is also seen in skin lesions of patients with BS.⁵

BS was reported to be associated with a higher incidence of *Streptococcus* mediated tonsillitis, and its adjuvant action to autoimmune disease cannot be excluded.⁶ Circulating immune complexes are thought to precipitate a neutrophilic vascular reaction, resulting in mucocutaneous lesions.^{7,8} A decrease in serum IgG and IgM was noted during co-trimoxazole treatment.²

Co-trimoxazole treatment was started with a daily dose of 50 mg/kg given in four divided doses (960 mg \times 4/day) for the first 3 days. Then the dose was reduced to 960 mg \times 3/day given for 1 week, followed by two double strength tablets a day until 6 weeks of treatment. The pustular rash gradually disappeared (figs 1A and B). After 6 weeks of the co-trimoxazole treatment the drug was stopped and weekly methotrexate injections were restarted at the previous dose. Knee effusion has relapsed only once during 1 year of follow up.

Evidence, that infection is the most probable environmental trigger of inflammatory joint disease is controversial, but interest in the topic is growing. The relationship between infection and collagen disease may be more subtle and complex than one of simply responding to Koch's postulates.⁹ Multiple infectious triggers which attack at an unknown rate, the delayed interval between infection and disease onset, and a role for primary, secondary, and persistent infection in the perpetuation of collagen

disease are the substance of the microbiology of rheumatic diseases. Bacteria are not only a source of exogenous antigens, which potentially cross react with those of the host, but can also exert adjuvant effects and release self antigens. Lipopolysaccharides, peptidoglycans, and bacterial DNA activate the innate immune system through specialised pattern recognition receptors of the Toll-like receptor family.¹⁰ Such microbial determinants are referred to as "pathogen associated molecular patterns". These patterns, together with the self antigens, activate the production of polyreactive antibodies, cytokine, and chemokines. Infected pustules of Behçet's disease might cause severe activation of the autoimmune response. Co-trimoxazole may be a promising treatment for controlling the microbial inductors and autoimmune reactions.

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Authors' reply

We thank Dr Rozin for his interest in our article and sharing his experience about a patient with Behçet's syndrome (BS) who improved with co-trimoxazole. We also recently had a patient with BS who had severe pustulosis, arthritis, oral and genital ulcers and who similarly did well with antibiotics. *Staphylococcus aureus* grew from

both the dermal pustules and the pustular pathergy lesions.

Thus far there have been few formal studies of antibiotic use in BS. Çalgüneri *et al* reported that penicillin treatment was beneficial for the mucocutaneous lesions¹ and arthritis.² A similar beneficial effect was observed with minocycline, which reduced both the frequency of clinical symptoms and the production of inflammatory cytokines by peripheral blood mononuclear cells stimulated by streptococcal antigens.³

The issue of an infectious aetiology in BS has also long been discussed. Behçet himself proposed a viral aetiology.⁴ It has been suggested that viruses, such as herpes simplex virus⁵ and parvovirus,⁶ and bacteria including various streptococcal strains⁷ and staphylococci⁸ have a role.

In one study peripheral $\gamma\delta$ +CD8+T cells of patients with BS showed a significantly proliferative response to the *Streptococcus sanguis* strain KTH-1.⁷ In another, T cells from patients with BS produced interferon γ when stimulated with staphylococcal superantigens.⁸ Clinical evidence for the role played by an infectious agent in pathogenesis includes the presence of a higher incidence of chronic tonsillitis and dental caries in patients with BS,⁹ observation of exacerbations of BS symptoms after acute episodes of infection with *Streptococcus agalactiae* vaginitis,¹⁰ and gingival infections with methicillin resistant *Staphylococcus aureus*.¹¹

There are also reports from our group showing the association of papulopustular lesions with arthritis in BS, suggesting a reactive type of arthritis.^{12,13} Lehner and colleagues suggested that a common antigen such as a stress protein might be involved.¹⁴ A significant increase of IgA antibodies to mycobacterial 65 kDa heat shock protein (HSP) in the serum of patients with BS was shown. Owing to the significant homology between mammalian and microbial HSPs, it is suggested that recurrent exposure to HSP may cause bacterial HSP responsive T cells to stimulate autoreactive T cells by cross reactivity mechanisms. In turn, these T cells might produce Th1-like proinflammatory and/or inflammatory cytokines, leading to tissue injury.

Whatever the precise pathogenic pathways will turn out to be, it is clear that further controlled trials with antibiotics in BS are warranted.

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Different threshold for prolactin response to hypoglycaemia in patients with rheumatoid arthritis?

In this issue of the *Annals* Eijsbouts and coworkers¹ show that the prolactin (PRL) response to hypoglycaemia is lower in patients with early untreated rheumatoid arthritis (RA) than in healthy controls. Furthermore, the unique design of their study allowed the authors to compare the PRL response before the test, after 2 weeks of treatment with a non-steroidal anti-inflammatory drug (NSAID) and, then again, after 6 months of conventional antirheumatic treatment with NSAIDs and disease modifying antirheumatic drugs (DMARDs). After 6 months they found that the PRL response to hypoglycaemia was significantly normalised, which correlated positively with the Disease Activity Score. The results of the study¹ suggest that disease activity and/or treatment with DMARDs significantly affects the central regulation of PRL secretion resulting from stimulation in patients with RA.

A possible involvement of PRL in the pathogenesis of inflammatory diseases has been intensively studied, including a hypothesis about dysregulated secretion of this pituitary hormone in patients with RA.² It has been shown that about one third of patients with RA are hyperprolactinaemic under basal conditions.² However, controversy remains about whether stimulated

secretion of PRL is up regulated or down regulated. Using the same stress stimulus as in the study of Eijsbouts *et al*,¹ we showed that the PRL response to hypoglycaemia was decreased in 38 patients with long term RA with moderate disease activity who were receiving treatment with NSAIDs or DMARDs.³ In line with others,^{4,5} we observed a PRL response to thyrotropin releasing hormone stimulation comparable to the response in healthy subjects in the same cohort of patients,³ suggesting a normal pituitary gland but altered central neuroendocrine regulatory mechanisms in patients with moderately active RA. The disease activity rather than the treatment itself seems have a more important effect on the PRL response to hypoglycaemia.

The PRL response to insulin-induced hypoglycaemia, unlike that of other pituitary hormones (for example, growth hormone), is not usually triggered in all healthy subjects, at least in a dose of 0.1 IU/kg of rapid acting insulin and may depend on an individual person's threshold for PRL release.⁶

In our most recent study we observed a lower PRL response to hypoglycaemia in glucocorticoid naive premenopausal patients with RA. When we analysed the data we found during hypoglycaemia that a double or higher increase of plasma PRL occurred only in 5/15 (33%) patients with RA but in 8/14 (57%) controls. PRL responses were irrespective of any clinical (disease activity, disease duration) or biochemical (tumour necrosis factor α , interleukin 6, C reactive protein, erythrocyte sedimentation rate) variables. The prevalence of PRL responders was not significantly different in patients with RA and controls, probably owing to the small sample size; however, the area under the response curve of PRL in patients with RA was significantly lower than in healthy controls.⁷ Nevertheless, we suggest that patients with RA may have a tendency towards a higher threshold for PRL release in response to hypoglycaemia, which deserves further investigation.

To test our proposal we would be interested in having the authors' view of their data in patients with RA and finding out whether the improvement in the PRL response in their study¹ was due to a quantitatively higher response in individual patients or rather a qualitative shift from being a PRL non-responding subject to a PRL responding subject.

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Authors' reply

We thank the authors for their interest in our work and opportunity for discussion of this interesting but still puzzling subject. Published reports are contradictory, possibly because of different study subjects, different methods of stimulating prolactin (PRL) secretion, and large variation of PRL levels between individual subjects.

Indeed the study mentioned by the authors¹ showed that about one third of patients with rheumatoid arthritis (RA) were hyperprolactinaemic under basal conditions, and in our article we refer to other studies reporting hypersecretion of prolactin in RA. However, by now we have performed three studies in which we could not confirm this: (a) the study that is now being discussed, including a total of 50 patients with RA; (b) a former smaller study in patients before and after undergoing total hip replacement,³ in which 10 patients with RA were compared with patients with osteoarthritis; and (c) a study in which we treated nine patients with RA with quinagolide, a dopamine agonist, which suppresses PRL secretion.⁴ None of these patients had raised PRL levels under basal conditions.

In our current study,² 17/20 (85%) healthy subjects had a double or higher increase in PRL levels in response to hypoglycaemia-induced stress, unlike the findings of the authors in their study, who found that only 57% of controls had a double or higher increase of PRL. They found PRL responses in patients with RA irrespective of disease activity, whereas in our study, as mentioned in the article, we found a negative correlation of PRL response and disease activity (DAS). We agree with the authors that it seems likely that disease activity is a more important factor in the changed PRL response than the treatment itself.

To answer the last question of the authors. In patients with RA we found that eight (40%) patients did not show a double or higher increase of PRL levels, and after treatment for 6 months only four did not show such a response, which could be consistent with the suggestion of Dr Imrich that more patients become PRL responding. However, 15/20 patients showed a marked increase in PRL levels after 6 months in response to hypoglycaemia-induced stress, and so we conclude that the improvement of the PRL response that we observed was