PostScript

MATTERS ARISING

Is IV infliximab better than IV methylprednisolone for the treatment of patients with RA when methotrexate fails?

A recent paper described a randomised comparative study of intravenous (IV) pulse methylprednisolone versus infliximab treatment in patients for whom methotrexate treatment had failed.[1] The conclusions that infliximab treatment offered substantial benefits over IV methylprednisolone may be correct, but the design of the trial has resulted in a biased assessment in favour of IV infliximab treatment. In addition, the failure of the IV methylprednisolone treatment to alter significantly a number of clinical and laboratory measures, including serum C reactive protein levels, is at odds with published reports.[2–7]

A comparison between the patient group in that study[1] and our previous papers on the use of IV methylprednisolone treatment[2 3 6] suggests that the patients in each study had similar disease duration, seropositivity, and clinical and laboratory measures of disease activity. Two main differences between the two patient groups are the background corticosteroid use (none in our study and most patients in the study by Durez *et al*) and the use of methotrexate. It has been our anecdotal experience that patients receiving long term oral corticosteroids do not respond as well, or for as long, to IV methylprednisolone as do patients who are not receiving oral corticosteroids and may require more frequent administrations of IV methylprednisolone for the same effect. However, I am not aware of any published data to support this. Whether this might explain the lack of response to IV methylprednisolone in the study by Durez *et al* is unclear.

In addition, the comparison between a single dose of IV methylprednisolone and three infliximab infusions, while reflecting the authors' usual clinical practice, is certainly a comparison biased in favour of the infliximab treated patient group. It should be remembered that there are no published data to validate the requirement for infliximab infusions at 0, 2, and 6 weeks. Some evidence suggests that a more sustained response to daily infusions of 1000 mg methylprednisolone succinate for 3 days rather than a single IV infusion is preferable, and our own studies showed a mean duration of response of only 5.1 weeks, suggesting that repeated infusions with IV methylprednisolone might have resulted in more benefit from this treatment. It might have been better for the authors to compare either consecutive daily infusions for 3 days or monthly infusions of IV methylprednisolone, especially as the main outcome measures were at week 14 after treatment.

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Authors' reply

We thank Dr Smith for his comments on our study,[1] which were largely addressed by Buttgereit *et al*.[2] As already answered, the lack of significant response to intravenous methylprednisolone in our group of patients with rheumatoid arthritis (RA) is probably related to their disease severity, reflected by their previous treatments.

As an alternative hypothesis, suggested by Dr Smith, we can also speculate that our patients belong to a corticosteroid resistant RA subset. The mechanisms of resistance to steroids are unknown in RA but have recently been explored in patients with asthma.[3]

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Antimicrobial treatment for *Chlamydia* induced reactive arthritis

We read with interest the article entitled ''Three month treatment of reactive arthritis with azithromycin: a EULAR double blind, placebo controlled study''.[1] The trial of Kvien *et al* suggests that weekly administration of azithromycin for 3 months is not efficacious in ameliorating the symptoms of reactive arthritis (ReA). Although this point seems clear, the authors then make a leap of faith and suggest that ''this study does not support the prolonged use of antibiotics for the alleviation of ReA''. There are several problems with this generalisation.

As Kvien *et al* correctly point out, polymerase chain reaction technology has documented the presence of *Chlamydia* and other causative organisms in the synovial tissue of patients with ReA.[2] This same technology has convincingly shown both in vitro and in vivo evidence of persistent metabolically active *Chlamydia*.[2] The data on post-dysentery organisms have repeatedly demonstrated bacterial fragments,[3] but viability has only been suggested in the case of *Yersinia*.[4] This makes a strong argument for the use of antimicrobial agents in post-chlamydial ReA, yet both patients with post-venereal and post-dysentery ReA were included in this trial.

Previous therapeutic trials also suggest that post-chlamydial ReA is more susceptible to antimicrobial treatment than the post-dysentery form. A 1991 trial suggested that lymecycline was an effective treatment for post-chlamydial ReA, but not for the post-dysentery form.[5] A subgroup analysis of post-chlamydial patients in another trial assessing

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 1β 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 spondyloarthropathy 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 co-trimoxazole (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,