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 raised 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 inflammatory marker levels, is at odds with published reports.2,3

A comparison between the patient group in that study1 and our previous papers on the use of IV methylprednisolone treatment2,4 suggests that the patients in each study had similar disease duration, severity, and disease activity, as confirmed by means of the DAS28 score. Both studies were randomised controlled trials and used 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, suggesting that repeated 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 of 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 1 or 2 days or daily 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, which were largely addressed by Burtger et al.1 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 also can speculate that our patients belong to a corticosteroid resistant RA subset. The mechanisms of resistance to corticosteroids are unknown in RA but have recently been explored in patients with asthma.4

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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.2 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.3 This same technology has convincingly shown both in vitro and in vivo evidence of persistent metabolically active Chlamydia.4 The data on post-dysentery organisms have repeatedly demonstrated bacterial fragments,5 but viability has only been suggested in the case of Yersinia.6 This makes a strong argument for the use of antimicrobial agents in post-chlamydial ReA, yet both patients with post-venerreal and post-dysenteric ReA were included in this trial.

Previous therapeutic trials also suggest that post-chlamydial ReA is more susceptible to antimicrobial treatment than the post-dysenteric form. A 1991 trial suggested that lymecycline was an effective treatment for post-chlamydial ReA, but not for the post-dysenteric form.7 A subgroup analysis of post-chlamydial patients in another trial assessing

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ciprofloxacin showed a trend towards improvement. 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. 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 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, which was overcome when a combination of antibiotic therapy was employed in the selection of the optimal drug. Its effectiveness that has been documented in vitro, dramatic response in the patients who were treated with a combination of ciprofloxacin and azithromycin in vitro. Artemic Antimicrob Agents Chemother 2005;49:3001–8.


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 previously and its effectiveness for some patients with Wegener’s granulomatosis associated with severe neutrophilic activation, which is also seen in skin lesions of patients with BS. BS was reported to be associated with a higher incidence of Streptococcus mediated tonsillitis, and its adjuvant action to auto-immune disease cannot be excluded. Circulating immune complexes are thought to precipitate a neutrophilic vascular reaction, resulting in pustular lesions in mucocutaneous conditions. A decrease in serum IgG and IgM was noted during co-trimoxazole treatment. Co-trimoxazole treatment was started with a daily dose of 50 mg/kg given in four divided doses (960 mg×4/day) for the first 3 days. Then the dose was reduced to 960 mg×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. 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 can 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 specialized pattern recognition receptors of the Toll-like receptor family. Such microbial determinants are referred to as “pathogen associated molecular patterns”. These patterns, together with the self antigens, activate the production of proinflammatory cytokines, antibodies, and chemokines. Infected pustules of Behcet’s disease might cause severe activation of the autoimmune response. Co-trimoxazole may be a promising treatment for controlling the microbial invaders 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 pterygium lesions.

Thus far there have been few formal studies of antibiotic use in BS. Calgine et al reported that penicillin treatment was beneficial for the mucocutaneous lesions and arthritis. 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.

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

In one study peripheral γδTCD8+T cells of patients with BS showed a significantly proliferative response to the Streptococcus sanguis strain KTH-1. In another, T cells from patients with BS produced interferon γ when stimulated with staphylococcal superantigens. 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, observation of exacerbations of BS symptoms after acute episodes of infection with Streptococcus agalactiae vaginitis, and gingival infections with methicillin resistant Staphylococcus aureus.

There are also reports from our group showing the association of papulopustular lesions with arthritis in BS, suggesting a reactive type of arthritis. Lehrer and colleagues suggested that a common antigen such as a stress protein might be involved. 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 these patients, 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 from this and other further controlled trials with antibiotics in BS are warranted.

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References


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


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

In this issue of the Annals Eijsbout and coworkers1 show that the prolactin (PRL) response to hypoglycaemia is lower in patients who have not yet been treated with antirheumatic drugs (DMARDs) 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 DiseaseActivity 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.3 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 Eijsbout 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.4 In line with others,1,4 we observed a PRL response to thyrotropin releasing hormone stimulation comparable to the response in healthy subjects in the same cohort of patients,5 suggesting a normal pituitary gland but altered central neuroendocrine regulatory mechanisms in patients with moderate disease activity of RA. The disease activity rather than the treatment itself seems to 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.7 When we analysed the data we found that hypoglycaemia in patients who had 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.8 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 early untreated rheumatoid arthritis, which 10 patients with RA were compared with patients with osteoarthritis; and a study in which we treated nine patients with RA with quinagolide, a dopamine agonist, suggesting a normal PRL response, which we observed in our most recent study.9 None of these patients had raised PRL levels under basal conditions.

In our current study,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 and disease activity (in RA). 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 such a response, which could be consistent with the suggestion of Dr Imrich that more patients become PRL responding.
due to a general quantitatively higher response in most patients, and not a shift towards more patients being PRL responding.

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A costly therapeutic dilemma in tophaceous gout: is etanercept or rasburicase preferable?

Tausche et al described a case of severe tophaceous gouty arthritis, which was treated with etanercept. They showed that anti-tumour necrosis factor α (TNFα) treatment can reduce the incidence of gouty attacks, which corresponds with the observation that TNFα is activated in patients with gouty arthritis. Clearly, this is a costly symptomatic approach that is only in addition to the main treatment, which is lowering the serum uric acid (SUA) levels in order to deplete urate depots and prevent gouty attacks and joint damage in the long term.

In the case presented, uricosuric treatment could only lower SUA levels from 0.58 mmol/l to 0.36 mmol/l despite high doses of 2–3 g probenecid a day. This is in contrast with our experience. In our population of 95% under-secretors (defined as uric acid excretion in urine <6.0 mmol/day during normal diet) monotherapy with probenecid 500 mg twice daily lowers SUA levels by 35% (mean (SD) 0.17 (0.05) mmol/l), whereas probenecid 500 mg twice daily in combination with allopurinol 200 mg daily lowers SUA levels by 48% (0.27 (0.08) mmol/l) in patients with an adequate renal function (endogenous creatinine clearance >50 ml/min).

In the case presented by Tausche et al, we would like to suggest another option for treating patients with severe tophaceous gout—that is, treatment with rasburicase. This recombinant form of urate oxidase very effectively metabolises uric acid in allantoic, which dissolves readily and is excreted by urine. So far one patient has been treated by applying rasburicase and urate depots were readily depleted (Moolenburgh JD et al, unpublished paper).

In our opinion, for a case of severe tophaceous gout, when an expensive treatment is indicated, rasburicase should be considered as a potentially very effective treatment before using anti-TNFα.

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Authors’ reply

Like Reinders et al, we have found that in the defined “normal” population of undersecretors, conventional treatment (anti-inflammatory drugs) is not sufficient. When these critical cases of severe tophaceous gout, as presented by us, the multiple tophi in the tissue and joints contain around 50 g or more uric acid. Despite the escalation of antihyperuricaemic (uricosuric or uricosuric) drugs, the SUA levels cannot be lowered significantly because of uric acid mobilisation from these depots and secondary shift to the serum.

Therefore, measurement of SUA levels alone does not verify the efficiency of treatment. In our view of our own experience (unpublished data), we agree with Reinders et al that the recombinant urate oxidase rasburicase should be introduced into the treatment of severe tophaceous gout if conventional uric acid lowering treatment is not effective or contraindicated. These cases are extremely rare and occur in under 0.01% of the population of undersecretors.

There are two principles in the treatment of gout: firstly, uric acid lowering treatment with uricosuric and uricosuric agents and, secondly, anti-inflammatory treatment of gouty attacks. Both of these treatment regimens should follow a “step scheme”.

In the uric acid lowering treatment rasburicase might rank as the last step in treatment of patients with tophaceous gout. When gouty arthritis is refractory to treatment (with non-steroidal anti-inflammatory drugs, steroids, opioids) it is useful to introduce tumour necrosis factor α (TNFα) blockade, as we showed in the published case. Because two different principles of action can follow there seems to be no need to answer the question of priority of one of these treatments. Rasburicase should not be considered before TNFα blockade but, rather, the two should be combined if conventional treatment is not sufficient.

The main dilemma of both treatments in the first instance is not the high cost but the missing approval by the FDA in severe tophaceous gout. Unfortunately, valid data are lacking, for instance, about the best way of application (dosage, application interval) owing to the absence of clinical studies. Shortly after infusion of rasburicase instant uric acid metabolism with abrupt decrease of SUA is observed. The resultant shift of uric acid from tissues to blood may cause a higher intensity of gouty attacks, and as we observed in one patient with urate nephropathy the worsening of renal function. We are very interested to learn of the article proposed by Moolenburgh et al. stecco TH. Hyperuricemic nephropathies. Nephron 1999;81:45–9.

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We regret that table 5 of this paper mentioned on p 101 was omitted. This can now be found on the web at http://www.annrheumdis.com/supplemental

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