EXTENDED REPORT

A randomised placebo controlled trial of delipidated, deglycolipidated *Mycobacterium vaccae* as immunotherapy for psoriatic arthritis

N Dalbeth, S Yeoman, J L Dockerty, J Highton, E Robinson, P L Tan, D Herman, F M McQueen

Ann Rheum Dis 2004;63:718–722. doi: 10.1136/ard.2003.007104

See end of article for authors' affiliations

Correspondence to:
Dr N Dalbeth, Department
of Immunology, Imperial
College London,
Hammersmith Campus, Du
Cane Road, London W12
0NN, UK;
n.dalbeth@ic.ac.uk

Accepted 14 June 2003

Objectives: To test the hypothesis that PVAC, delipidated, deglycolipidated heat killed *Mycobacterium vaccae*, is an effective and safe treatment for psoriatic arthritis (PsA). This treatment has shown promising results in psoriasis.

Methods: 36 patients with PsA in two centres were studied in this double blind, placebo controlled, randomised trial. Patients were randomised to receive two intradermal injections of 50 µg PVAC or placebo and were followed up for 24 weeks. The primary end point was the Psoriatic Arthritis Response Criteria (PsARC), a composite measure based on changes in joint tenderness and swelling scores and physician and patient global assessments.

Results: The PsARC response at either 12 or 24 weeks was achieved by 9/18 (50%) placebo and 9/18 (50%) PVAC patients ($p = 1.0$). No significant differences in the Psoriasis Activity and Severity Index (PASI), patient or physician global assessments, CRP, or Health Assessment Questionnaire score over time were found between the two groups. However, changes in the pain visual analogue scale over time did differ between the two groups ($p = 0.006$): at 24 weeks the mean score in the PVAC group had declined by 19.2 mm and in the placebo group had increased by 4.8 mm. PVAC was well tolerated with no increased incidence of adverse events compared with placebo.

Conclusions: PVAC was not shown to be as effective as immunotherapy for PsA. The striking response to placebo in this study reinforces the importance of adequately controlling therapeutic trials in PsA.

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that affects 7–42% of patients with psoriasis^{1,2} and causes significant pain and disability.³ To date, treatments for PsA—namely, non-steroidal anti-inflammatory drugs (NSAIDs) and traditional disease modifying antirheumatic drugs (DMARDs), have not been universally efficacious and may be associated with significant side effects.^{4–7} More recently, anti-tumour necrosis factor α (TNF α) treatment has been shown to be effective for active PsA and psoriasis.⁸

In 1998, a new therapeutic agent, PVAC, was investigated for the treatment of psoriasis. PVAC consists of delipidated, deglycolipidated heat killed *Mycobacterium vaccae* (*M vaccae*) and was originally studied as a vaccine to prevent tuberculosis and leprosy in the Philippines. The trials in psoriasis were started after the observation that the psoriasis skin lesions of patients with leprosy and psoriasis apparently improved when they were given mycobacterial vaccines.⁹ To explore this further, an open label study of PVAC for treatment of psoriasis was conducted.¹⁰ In this study two 50 µg doses of PVAC were given intradermally to 20 adult patients with moderate to severe psoriasis (Psoriasis Activity and Severity Index (PASI)¹¹ score 12–35). By 12 weeks, 13/20 (65%) patients had improved with a >50% fall in their PASI score. In 30%, complete remission was attained. No abnormal laboratory findings were noted in patients receiving PVAC, but local reactions developed at the site of injections and gradually resolved over 4 weeks. One patient with erythrodermic psoriasis experienced a flare of this condition. In addition, a placebo controlled trial of unmodified *M vaccae* for chronic plaque psoriasis has reported significant benefits in those patients receiving active treatment.¹²

The possible mechanisms of action of PVAC in psoriasis have been investigated. Biopsies of the PVAC injection site

show a classical delayed-type hypersensitivity response with recruitment of dendritic cells, macrophages, and T cells into the dermis. In vitro studies with PVAC show that it stimulates dendritic cell activity, enhancing antigen presenting function. Cells from the human mononuclear cell line THP-1 can phagocytose fluorescein labelled PVAC, which stimulates them to produce interleukin 10 (IL10). This in turn has an inhibitory effect on T cell function, decreasing production of interferon gamma (IFN γ) (Tan PL *et al*, unpublished data). This change in the pattern of cytokine production may be of relevance for two reasons. Firstly, there is evidence that psoriasis is characterised by low IL10 levels in skin lesions.¹³ IL10 is a known inhibitor of TNF α ¹⁴ and, possibly, IL10 induced by PVAC has a beneficial effect on psoriasis by down regulating TNF α production. Secondly, IFN γ may have a role in the pathogenesis of psoriasis. When injected into the skin of normal subjects, IFN γ can induce keratinocyte hyperplasia and lesions similar to psoriatic plaques.¹⁵ T cells are known to be crucial to the psoriatic disease process¹⁵ and are the main source of IFN γ . When T cells isolated from human psoriatic plaques are injected into severe combined immune deficient mice, they can transform normal human skin, previously transplanted into these animals, into psoriatic skin.¹⁶ Thus, if PVAC can reduce the production of IFN γ , then down regulation of the immune process causing psoriasis may occur.

Abbreviations: ACR, American College of Rheumatology; CRP, C reactive protein; DMARDs, disease modifying antirheumatic drugs; IFN γ , interferon γ ; IL, interleukin; NSAIDs, non-steroidal anti-inflammatory drugs; PASI, Psoriasis Activity and Severity Index; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Criteria; TNF α , tumour necrosis factor α

The suggestion that T cells have a pivotal role in the pathogenesis of PsA as well as psoriatic skin disease is supported by the observation that large numbers of CD4+ T cells of the CD45RO phenotype are present in PsA synovial membrane.¹⁷ Interestingly, there is also some evidence that IFN γ plays a part in PsA. Three patients with psoriasis, given recombinant IFN γ as an immunomodulatory agent, experienced a flare of PsA after 3–4 months of treatment. In one, re-treatment with IFN γ resulted in further joint inflammation.¹⁸ This suggests that down regulation of IFN γ production by PVAC might also be expected to have a beneficial effect in PsA.

On the basis of both clinical and laboratory data, we designed a randomised, double blind, placebo controlled trial to test the hypothesis that PVAC is a safe and effective treatment for PsA.

METHODS

Subjects

Eligible subjects were men and women aged 18–75 years with psoriasis and PsA (as diagnosed by a rheumatologist). All patients had active disease, defined as three or more tender joints and three or more swollen joints.⁸ All patients had disease duration of more than 6 months and were rheumatoid factor negative. Women of childbearing potential agreed to the use of adequate contraception throughout the study.

Subjects were excluded if they had severe psoriasis (pustular, erythrodermic, or exfoliative), clinically relevant cardiovascular, hepatic, neurological, endocrine, or other major systemic disease, axial disease only, inflammatory bowel disease, or reactive arthritis. Subjects were also excluded if they had received PUVA, other UV treatment, prednisone >10 mg/day, intra-articular steroid, or DMARD treatment (including methotrexate, sulfasalazine, cyclosporin A) in the 4 weeks before administration of PVAC. Topical treatments, oral NSAIDs, and low dose corticosteroids were permitted throughout the study.

The local ethics committee approved this study and all patients provided written informed consent.

Study design

The trial was a double blind, randomised, placebo controlled study conducted at two centres in New Zealand. Patients were recruited from outpatient rheumatology clinics from November 2000 to November 2001. The randomisation scheme was generated before the study, with a block size of eight at each centre and with equal numbers of subjects assigned to each treatment group. Randomisation was performed by allocation of computer generated random numbers.

Subjects were assigned to receive 0.1 ml intradermal injections of 50 μ g PVAC or placebo (0.9% NaCl) at weeks 0 and 3. PVAC (Corixa, Seattle USA) was supplied and randomised by Genesis Research & Development Corporation Limited, Auckland, New Zealand. All preparations were identical in appearance. The treatment assignments were not released until all aspects of the study were completed. Two independent rheumatologists reviewed safety throughout the trial.

Subjects were initially assessed at a screening visit to determine eligibility for the trial. Those patients receiving DMARDs then underwent a 4 week washout period. At the follow up visit (week 0), these patients were rescreened, and baseline clinical examination and investigations were performed. The first intradermal injection of PVAC or placebo was also given on this visit. Plain radiographs of the hands and feet were obtained upon entry into the trial. Follow up was at 3 weeks (when the second injection was given) and then at 8, 12, and 24 weeks. At each visit, clinical assessments included swollen joint count (maximum score 66

joints), tender joint count (maximum score 68), PASI score, patient and physician questionnaires, and blood tests. Injection site reactions were measured by a person not assessing clinical response. The site of injection was covered by gauze for all subjects before clinical assessment and subjects were advised on each visit that there was no relationship between the size of the injection site reaction and psoriasis response in previous studies.

Efficacy measurements

The primary outcome was the proportion of subjects meeting the Psoriatic Arthritis Response Criteria (PsARC) at 12 or 24 weeks. This composite measure requires improvement in two factors (with at least one being a joint score) with worsening in none, of the following four factors: patient and physician global assessments (improvement defined as a decrease by ≥ 1 unit; worsening defined as an increase in ≥ 1 unit on a 0–5 Likert scale); and tender and swollen joint scores (the sums of all joints scored; improvement defined as a decrease by more than $\geq 30\%$; worsening defined as an increase $\geq 30\%$).⁶

A secondary end point was the proportion of subjects meeting the ACR20 (the American College of Rheumatology preliminary criteria for improvement of rheumatoid arthritis¹⁹) at 12 or 24 weeks. Other secondary end points were changes in the ACR20 core set variables, the number of withdrawals, and the change in the PASI score from baseline at weeks 12 and 24.

Safety assessments

Safety was monitored by physical examination, vital signs, and laboratory tests. All possible adverse events were recorded, with details of severity and likely causality.

Statistical analysis

All analyses were conducted independently of the manufacturers and suppliers of PVAC, and according to an intention to treat principle with the use of two tailed tests and an α value of 0.05. Repeated measures using a mixed model approach²⁰ were used to investigate whether outcomes differed over time and between placebo and drug groups. Initial measures such as age, sex, weight, duration of psoriasis and PsA, DMARD use, nail disease, and axial disease were included as covariates in analyses.

Power calculations based on a PsARC response in the placebo group of 23% as reported by Mease *et al*⁸ showed that a sample size of 18 in each group had 80% power at the 0.05 level of significance to detect a change in response in the treatment group from 23% to 50%, assuming that the placebo group remained unchanged, the correlation between repeated measures was 0.02, and the trial had five time points.

The SAS statistical package²¹ was used as it incorporates procedures for mixed models for continuous, ordinal, and binary outcomes.

RESULTS

Baseline characteristics

Fifty one patients were screened for entry into the study, of whom 15 were not enrolled because they did not meet entry criteria (five unable to undergo DMARD washout, three without active disease, two with inflammatory bowel disease, and five with miscellaneous causes).

Therefore, 36 patients (16 female) entered the trial. Of these, 18 received PVAC and 18 received placebo. Table 1 summarises their baseline demographic, clinical, and laboratory data. The median age was 43 years (range 23–72). The median duration of psoriasis was 18 years (1–41) and of PsA 10 years (1–40). Thirteen patients had asymmetric oligoarthritis and 23 symmetric polyarthritis. Axial disease was

Table 1 Baseline characteristics of the patients studied

Characteristic	PVAC (n = 18)	Placebo (n = 18)
Age (years), mean (SD)	40.6 (8.8)	51.8 (11.8)
Female sex, No (%)	6 (33)	10 (56)
Duration of psoriasis (years), median (range)	13 (1–35)	20.5 (2–41)
Duration of PsA (years), median (range)	9 (1–20)	10 (2–40)
DMARDs (before washout) at onset, No (%)	4 (22)	11 (61)
Methotrexate (before washout) at onset, No (%)	1 (6)	10 (56)
Asymmetric oligoarticular disease, No (%)	10 (56)	3 (17)
Polyarticular disease, No (%)	8 (44)	15 (83)
Axial disease, No (%)	7 (39)	7 (39)
Erosions on hand/feet radiographs, No (%)	6 (33)	7 (39)
Tender joint count, median (range)	15.5 (4–42)	16.5 (5–50)
Swollen joint count, median (range)	9.5 (3–27)	11.5 (3–33)
Patient global assessment, median (range)	2.5 (2–4)	2 (1–4)
Physician global assessment, median (range)	3 (1–4)	3 (1–4)
Patient pain score, mean (SD)	46.1 (19.9)	46.7 (24.4)
CRP (normal <1 mg/l), median (range)	7.5 (2.0–39.0)	9.5 (1.0–62.0)
HAQ, median (range)	0.875 (0.0–1.625)	0.75 (0.0–2.5)
PASI, median (range)	2.8 (0.2–11.7)	2.5 (0.5–18.6)

DMARDs, disease modifying antirheumatic drugs; CRP, C reactive protein; HAQ, Health Assessment Questionnaire; PASI, Psoriasis Activity and Severity Index.

present in 14 patients. Erosive changes were present on hand and feet radiographs in 13 patients. The median active joint counts at baseline were 16 tender joints (4–50) and 11 swollen joints (3–33). There were some differences between the two groups: those patients receiving PVAC were younger, had more oligoarticular disease, and were less likely to be receiving DMARDs at the time of entry into the trial.

Primary end points

At 12 weeks, the PsARC response was achieved in 7/18 patients receiving placebo and 6/18 receiving PVAC ($p = 0.7$). At 24 weeks, the PsARC response was achieved in 8/18 patients receiving placebo and 6/18 receiving PVAC ($p = 0.5$). The PsARC response at either 12 or 24 weeks was achieved by 9/18 (50%) placebo and 9/18 (50%) patients receiving PVAC ($p = 1.0$) (table 2). A repeated measures analysis including the patient characteristics used in the analysis of individual measures found no evidence of a change over time ($p = 1.0$) or a difference between two treatment groups ($p = 0.5$) in the PsARC response.

Secondary end points

Table 3 summarises the ACR20 and PASI results. The ACR20 response at 12 and/or 24 weeks was achieved by 3/18 placebo and 5/18 PVAC treated patients ($p = 0.4$). There was no difference between the two groups for changes in the patient global assessment, physician global assessment, swollen joint count, tender joint count, C reactive protein (CRP) or Health Assessment Questionnaire. However, changes in the pain visual analogue score over time did differ between the two groups ($p = 0.006$); at 24 weeks the mean score in the placebo group had increased by 4.8 mm and in the PVAC group had declined by 19.2 mm (fig 1).

Table 2 Primary end point: number of patients achieving the PsARC response

Week	PVAC (n = 18)	Placebo (n = 18)	p Value
12	6	7	0.7
24	6	8	0.5
12 and/or 24	9	9	1.0

There was no evidence that the changes in the PASI over time differed between the two groups; an improvement in the PASI score of $\geq 50\%$ at week 12 and/or week 24 was present in 5 (28%) patients receiving placebo and 8 (44%) patients receiving PVAC ($p = 0.3$).

Four patients in the placebo group and three in the PVAC group withdrew from the study ($p = 0.7$). In all cases, the reason for withdrawal was lack of efficacy.

Safety

Adverse events were reported in five placebo treated patients and four PVAC treated patients ($p = 0.7$). The adverse events recorded for the PVAC treated patients were menstrual irregularity (two patients), fatigue, and influenza.

Injection site reactions

Injection site reactions, defined as skin induration >0 cm within 3 weeks of injection, were found in 6/18 (33%) placebo treated patients and 17/18 (94%) PVAC treated patients ($p < 0.001$).

DISCUSSION

There has been considerable interest in the use of vaccine treatment for the treatment of inflammatory disorders.^{22–24} However, this double blind, placebo controlled trial did not show that PVAC as immunotherapy alters the clinical activity of PsA. This trial was powered to detect only large differences between PVAC and placebo. As far as we know this is the first study of *M vaccae* in PsA and if there were trends suggesting

Table 3 Secondary end points: (A) number of patients achieving the ACR20 response; (B) number of patients with improvement in the PASI score of $\geq 50\%$

Week	PVAC (n = 18)	Placebo (n = 18)	p Value
(A)			
12	2	2	1.0
24	3	2	0.6
12 and/or 24	5	3	0.4
(B)			
12	5	5	1.0
24	5	4	0.7
12 and/or 24	8	5	0.3

Figure 1 Change in pain visual analogue score (VAS) over time. Week 24, PVAC v placebo, $p=0.006$

efficacy, a larger study would be warranted. The current data do not support a more definitive study, unless a different dose or dosing regimen can be justified. PVAC does appear to be a safe treatment with no significant adverse events noted during the 6 month follow up period.

Although there are many similarities between the immunopathology of psoriasis and PsA, it is widely recognised that the activity of skin psoriasis and PsA do not always occur at the same time, suggesting that the immune mechanisms triggering skin and joint inflammation may be distinct. Hence, therapeutic agents that are immune modifiers may not be effective for both manifestations of psoriasis unless they target a common inflammatory pathway. This may explain why PVAC, a treatment shown to be effective for skin disease, has less impressive effects on the articular disease associated with psoriasis. Interestingly, a placebo controlled trial of IL10 in PsA showed significant improvements in skin disease, but not articular disease activity scores.²⁵

Despite previous studies showing beneficial effects of *M vaccae* in skin disease, this study found no difference between the two groups for the PASI, which reflects the severity of psoriasis. One explanation may be that in previous studies of PVAC in psoriasis,¹⁰ patients had much more severe psoriasis but very low rates of DMARD use, compared with the patients in our study. This study was not designed to investigate the efficacy of PVAC in psoriasis and, indeed, patients with PsA often have mild psoriasis.²⁶ The mean PASI score at the start of this trial was at the lower limits of the PASI scale and improvements other than total clearing may not have been detectable. The current study attempted to control for DMARD use by a 4 week washout before treatment. Another possible explanation for the lack of skin response to PVAC may be that slightly different physical characteristics of the PVAC preparations accounted for the variation in response. This phenomenon has been described in trials of oral tolerance.²⁷ Clearly such differences would potentially influence the effect of PVAC on both the skin and the joints in PsA.

When the two groups were compared, more patients in the placebo group were taking DMARDs at baseline. This finding may in fact strengthen our results, given that patients with severe disease are more likely to be treated with DMARDs. Therefore, the placebo treated group with possibly more severe disease had similar results to those with less severe disease receiving PVAC. Importantly, baseline variables including DMARD use, patterns of arthritis, and age were

included in the analysis models so that any differences noted are over and above baseline.

A potential confounding factor of this study may be that those patients receiving PVAC had greater and more frequent local skin responses to injection. The assessors were unaware of the severity of the skin reaction. Theoretically, this skin response may enhance a placebo effect. However, despite the differences in skin response, there was no difference between the two groups, again reinforcing the lack of benefit observed with PVAC.

The only benefit found in the PVAC group was improved pain scores at 24 weeks. Although interesting, it seems unlikely that this result is clinically significant given that there was no difference in pain scores at any other times and that this finding was not related to improvements in patient global assessments or other markers of inflammatory disease, such as CRP, swollen joint count, or tender joint count.

The most striking feature of this study is the large PsARC response to placebo. In the placebo group 50% of patients achieved a PsARC response at 12 and/or 24 weeks. This phenomenon has been reported in other trials. For example, in the Department of Veterans Affairs Cooperative Study comparing sulfasalazine and placebo in PsA, the PsARC response in the placebo group was 45% at 36 weeks.⁶ In the randomised controlled trial of etanercept in PsA, of those patients receiving placebo, 23% achieved the PsARC response at 12 weeks and 13% achieved the ACR20 response.⁸ The baseline swollen and tender joint counts were lower in this study than in the etanercept and sulfasalazine trials, and in this setting small fluctuations in the placebo treated group may have led to an apparent improvement in the PsARC response.

A recent Cochrane review also emphasised the large responses to placebo in PsA clinical trials. In this review, all trials assessed showed improvements in the placebo group over baseline, with pooled improvement of 0.39 disease index units (95% confidence interval 0.26 to 0.54). Overall, the effect size of the placebo response in the PsA group was three times greater than in the rheumatoid arthritis group.⁷ This enhanced response to placebo may be due in part to the fluctuating course of PsA. Our study strongly reinforces the importance of adequately controlling trials in PsA treatment.

In summary, immunotherapy in the form of a mycobacterial vaccine for PsA has not been shown to be effective. It is likely that more direct treatments targeting immune dysfunction in PsA will provide greater therapeutic benefits.⁸ As emphasised by this study, trials of new treatments should be carried out in the presence of adequate controls to account for the significant placebo response found in PsA.

ACKNOWLEDGEMENTS

The Health Research Council of New Zealand funded this study. P Tan and D Herman are employees of Genesis Research and Development Corporation Ltd, Auckland, New Zealand.

Authors' affiliations

N Dalbeth, S Yeoman, F M McQueen, Department of Rheumatology, Auckland Healthcare, Auckland, New Zealand
J L Dockerty, J Highton, Department of Rheumatology, Healthcare Otago, Dunedin, New Zealand
J Highton, Department of Medicine, University of Otago, Dunedin, New Zealand
E Robinson, School of Population Health, University of Auckland, Auckland New Zealand
P L Tan, D Herman, Genesis Research and Development Corporation Limited, Auckland, New Zealand

REFERENCES

- 1 Gladman DD. Natural history of psoriatic arthritis. *Baillieres Clin Rheumatol* 1994;8:379-94.

- 2 **Shbeeb M**, Uramoto KM, Gibson LE, O'Fallon WM, Gabriel SE. The epidemiology of psoriatic arthritis in Olmstead County, Minnesota, USA, 1982-1991. *J Rheumatol* 2000;**27**:1247-50.
- 3 **Husted JA**, Gladman DD, Farewell VT, Cook RJ. Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. *Arthritis Rheum* 2001;**45**:151-8.
- 4 **Espinoza LR**, Zakraoui L, Espinoza CG, Gutierrez F, Jara LJ, Silveira LH, et al. Psoriatic arthritis: clinical response and side effects to methotrexate therapy. *J Rheumatol* 1992;**19**:872-7.
- 5 **Farr M**, Kitas G, Waterhouse L, Jubb R, Felix-Davies D, Bacon PA. Sulphasalazine in psoriatic arthritis: a double-blind placebo-controlled study. *Br J Rheumatol* 1990;**29**:46-9.
- 6 **Clegg DO**, Reda DJ, Meijas E, Cannon GW, Weisman MH, Taylor T, et al. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. *Arthritis Rheum* 1996;**39**:2013-20.
- 7 **Jones G**, Crotty M, Brooks P. Interventions for psoriatic arthritis. *Cochrane Database Syst Rev* 2000;**3**:CD000212.
- 8 **Mease PJ**, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet* 2000;**356**:385-90.
- 9 **Ramu G**, Prema GD, Balakrishnan S, Shanker Narayan NP, Stanford JL. A preliminary report on the immunotherapy of psoriasis. *Indian Medical Gazette* 1990;**124**:381-2.
- 10 **Balagon MV**, Tan PL, Prestidge R, Cellona RV, Abalos RM, Tan EV, et al. Improvement in psoriasis after intradermal administration of delipidated, deglycolipidated *Mycobacterium vaccae* (PVAC): results of an open-label trial. *Clin Exp Dermatol* 2001;**26**:233-41.
- 11 **Fredricksson T**, Pettersson U. Severe psoriasis, oral therapy with a retinoid. *Dermatologica* 1978;**157**:238-44.
- 12 **Lehrer A**, Bressanelli A, Wachsmann V, Bottasso O, Bay ML, Singh M, et al. Immunotherapy with *Mycobacterium vaccae* in the treatment of psoriasis. *FEMS Immunol Med Microbiol* 1998;**21**:71-7.
- 13 **Asadullah K**, Sterry W, Stephanek K, Jasulaitis D, Leupold M, Audring H, et al. IL-10 is a key cytokine in psoriasis. Proof of principle by IL-10 therapy: a new therapeutic approach. *J Clin Invest* 1998;**101**:783-94.
- 14 **de Waal Malefyt R**, Abrams J, Bennet B, Figdor CG, de Vries JE. Interleukin 10 (IL-10) inhibits cytokine synthesis by human monocytes: an autoregulatory role of IL-10 produced by monocytes. *J Exp Med* 1991;**174**:1209-20.
- 15 **Barker JN**. The immunopathology of psoriasis. *Baillieres Clin Rheumatol* 1994;**8**:429-38.
- 16 **Wrone-Smith T**, Nickoloff BJ. Dermal injection of immunocytes induces psoriasis. *J Clin Invest* 1996;**98**:1878-87.
- 17 **Veale D**, Yanni G, Rogers S, Barnes L, Bresnahan B, Fitzgerald O. Reduced synovial membrane macrophage numbers, ELAM-1 expression, and lining hyperplasia in psoriatic arthritis as compared with rheumatoid arthritis. *Arthritis Rheum* 1993;**36**:893-900.
- 18 **O'Connell PG**, Gerber LH, Digiovanna JJ, Peck GL. Arthritis in patients with psoriasis on interferon. *J Rheumatol* 1992;**19**:80-2.
- 19 **Felson DT**, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum* 1993;**36**:729-40.
- 20 **Brown H**, Prescott R. *Applied mixed models in medicine*. New York: Wiley, 1999.
- 21 **Littell RC**, Milliken GA, Stroup WW, Wolfinger RD. *SAS system for mixed models*. Cary NC: SAS Institute Inc.
- 22 **Moreland LW**, Morgan EE, Adamson TC 3rd, Fronzek Z, Calabrese LH, Cash JM, et al. Cell receptor peptide vaccination in rheumatoid arthritis: a placebo controlled trial using a combination of Vbeta3, Vbeta14 and Vbeta17 peptides. *Arthritis Rheum* 1998;**41**:1919-29.
- 23 **Weiner HL**, Selkoe DJ. Inflammation and therapeutic vaccination in CNS disease. *Nature* 2002;**420**:879-84.
- 24 **Link H**, Huang YM, Masterman T, Xiao BG. Vaccination with autologous dendritic cells: from experimental autoimmune encephalitis to multiple sclerosis. *J Neuroimmunol* 2001;**114**:1-7.
- 25 **McInnes IB**, Illei GG, Danning CL, Yarboro CH, Crane M, Kuroiwa T, et al. IL-10 improves skin disease and modulates endothelial activation and leukocyte effector function in patients with psoriatic arthritis. *J Immunol* 2001;**167**:4075-82.
- 26 **Cohen MR**, Reda DJ, Clegg DO. Baseline relationships between psoriasis and psoriatic arthritis: analysis of 221 patients with active psoriatic arthritis. Department of Veterans Affairs Cooperative Study Group on Seronegative Spondyloarthropathies. *J Rheumatol* 1999;**26**:1752-6.
- 27 **Choy EH**, Scott DL, Kingsley GH, Thomas S, Murphy AG, Staines N, et al. Control of rheumatoid arthritis by oral tolerance. *Arthritis Rheum* 2001;**44**:1993-7.