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Leader

Dilemmas of low dosage glucocorticoid treatment in rheumatoid arthritis: considerations of timing

Controversy continues regarding relative benefits versus adverse effects of low dosage glucocorticoid treatment (LDGT) in rheumatoid arthritis.¹⁻⁵ Opinions differ on the definition of LDGT in patients with rheumatoid arthritis and its variations, depending upon age and gender. We believe that LDGT for rheumatoid arthritis is best considered in terms of ranges of physiological replacement, that is, up to 5 mg of prednisolone (or prednisone) daily for women and up to 7.5 mg for men in their active years, but less in the elderly of either gender.

Elderly females develop more adverse effects from chronic LDGT than young males, particularly osteoporosis,^{2,3,5} which may be related to an osteoporosis sparing⁶ and glucocorticoid protective⁷ role of androgens. Clinical experience (ATM) suggests that patients with rheumatoid arthritis presenting mainly with polymyalgia-rheumatica-like muscular and systemic manifestations respond relatively better to LDGT than those showing either more aggressive erosive synovitis processes or indications of necrotising vasculitis.

Another consideration in choosing glucocorticoid dosage levels and in assessing efficacy of LDGT is intrinsic differences between patients in the competence and responsiveness of their hypothalamic-pituitary-adrenal (HPA) glucocorticoid axis.⁸ A subset of patients with rheumatoid arthritis has baseline HPA axis or glucocorticoid action deficiencies.^{8,9} These patients are expected to benefit relatively more from LDGT than the remainder who have fully normal basal physiology, as may patients with insufficient endogenous HPA axis responsiveness to acute inflammatory mediators.^{10,11} Additionally, the overall severity of the disease itself and its response to alternative measures dictate the choice between LDGT or higher doses, when glucocorticoid treatment is employed.⁵

A single daily morning dose of LDGT is conventional. Evening or night time administration appears to exert greater suppression of morning ACTH and cortisol secretion than dosing in the morning hours.¹² Individual patients differ in their subjective responses to LDGT administration times, however, and some have better symptomatic relief from either night time or split morning and evening schedules than the conventional single morning dose.

In this issue, Arvidson and colleagues¹³ performed an exploratory study of the short term anti-inflammatory effects of "low dose" prednisolone (that is, four daily doses of either 5 or 7.5 mg) in treating active rheumatoid arthritis. Randomly allocated LDGT administrations at either 2.00 am (group A) or 7.30 am (group B) were compared. Clinical and laboratory indicators of rheumatoid arthritis disease activity were studied as outcome variables, at 7.30 am on day 5. The 2.00 am group (A) received their fourth and last prednisolone dose 5½ hours before outcome assessment at 7.30 am on day 5. In contrast, the 7.30 am group (B) received their fourth and last dose on the morning of day 4, that is, 24 hours before outcome assessment on day 5. Thus the study is not balanced in the timing of outcome assessments with respect to the alternative LDGT dosing schedules. Patient and physician assessments were made with knowledge of these alternative schedules. Therefore caution is needed in interpreting the results of this exploratory study.

The rationale for the 2.00 am dosing was an attempt to suppress more effectively the night time diurnal peaking of serum interleukin-6 (IL-6) concentrations which occurs both in normal^{14,15} and rheumatoid arthritis^{15,16} subjects. Such a circadian pattern of serum IL-6 was suspected to increase morning symptoms and other inflammatory sequelae in rheumatoid arthritis.¹³ The data are provocative and allow preliminary inferences to be raised concerning early *v* later phase responses of various rheumatoid disease activity manifestations to short term (four days) LDGT. Further and more strictly controlled studies will be required for accurate interpretation of the basic clinical-physiological effects of LDGT.

Before addressing results of this study, essential pharmacokinetic¹⁷ and biological actions¹⁸ of ingested prednisolone tablets should be emphasised. After oral administration, peak plasma concentration is usually achieved in 1-3 hours and the plasma half life is 2-3.5 hours.¹⁷ The biological half life (BHL) is estimated to be 6 hours.¹⁸ Given these essential pharmacological facts, superior direct effects of LDGT on the outcome of at least some rheumatoid activity measures in Arvidson's study would be expected in group A than with group B, that is,

following the shorter (1×BHL) rather than the longer (4×BHL) dose-response interval.

Responses found to be most prominent within 5½ hours of the last dose in this study,¹³ that is, “early phase” effects, may be attributable to both the direct acute mechanisms (those occurring within 1 BHL) of the fourth and last 2.00 am dose plus the accumulated subacute anti-inflammatory actions of the three preceding nightly doses. Responses which are similarly evident within 5½ hours and 24 hours following the last dose in this study, that is, given to either group A or B, may be considered mainly “later phase” effects resulting from cumulative actions of the preceding four doses.

Accepting the above considerations, the observed efficacy-response patterns to the 2.00 am *v* 7.30 am doses of LDGT in the Arvidson study may be interpreted as occurring within three categories. The first type shows clearly superior (and marked) effects following the shorter (5½ hours) than longer (24 hours) interval from the last dose. The second type shows similar (and moderate) effects following either interval from the last dose. The third type shows inconsistent (and minor) responses in both group A and group B. If the three types of observed efficacy-response patterns to LDGT are confirmed in a properly controlled, double blind, balanced dosing-outcome trial, then they may yield important clues to glucocorticoid actions upon various disease manifestations in rheumatoid arthritis during early (1×BHL) *v* later (4+×BHL) phases.

Type 1 (“early phase”) LDGT effects in active rheumatoid arthritis

The 2.00 am (group A) LDGT dosing was clearly superior to the 7.30 am (group B) dosing in regard to the monitored clinical variables, that is, morning stiffness (minutes); pain at rest (visual analogue score); and Lansbury and Ritchie indices. In each instance, mean responses of the 2.00 am group were at least 50% improved from baseline *v* less than 20% improvements in the 7.30 am group. Furthermore, the ratios of Δ improvements (that is, ratios of baseline to outcome measurements) were at least fourfold greater in the 2.00 am than 7.30 am dosing groups. The mean IL-6 concentration fell dramatically by 80% in the 2.00 am *v* 40% in the 7.30 am dosing group, both decrements being significant ($P < 0.01$ and $P < 0.05$, respectively).

Importantly, however, the dramatic type 1 improvements in morning clinical manifestations did not correlate significantly with the marked decrease in 7.30 am serum IL-6 concentrations in group A. Since IL-6 is both a proinflammatory^{11,19} and an anti-inflammatory^{20,21} cytokine, which might also participate in suppression of the inflammatory process in rheumatoid arthritis, such a lack of correlation could be understandable.

Type 2 (“later phase”) LDGT effects in active rheumatoid arthritis

Similar and at least 20% improvements in both group A and B occurred in the acute phase markers, that is, C reactive protein, serum amyloid-A (SAA) protein, and erythrocyte sedimentation rate (ESR). These biological markers of inflammation and disease activity in rheumatoid arthritis are increased by the inflammatory cytokines tumour necrosis factor α (TNF α), interleukin-1 (IL-1), and IL-6,^{11,22,23} and are decreased by glucocorticoid treatment.^{21,24} The degree of suppression of these acute phase inflammatory markers was not as great as for IL-6 or the type 1 clinical manifestations. The type 2, “later phase” responses may be interpreted as reflecting a relatively greater degree of indirect than direct LDGT suppression of inflammation. Perhaps the mechanisms result from

inhibitory actions on cell populations,¹¹ more than from direct physiological effects of LDGT on early phase type 1 responses.²⁵

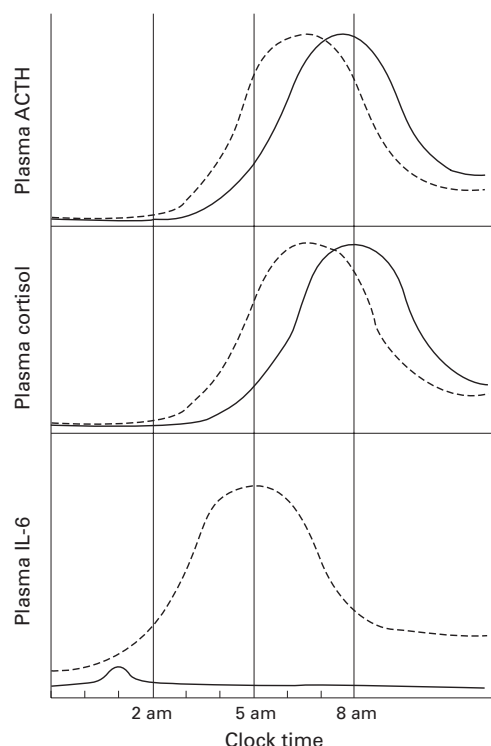
Type 3 (“inconsistent response”) LDGT effects in active rheumatoid arthritis

The remaining outcome variables in the last category of responses to short term LDGT showed Δ changes, which were either not consistent between the two administration groups in their direction or showed only minor changes (tables 1 and 2 in¹³). Responses were less than 20% in both groups (except for a 29.2% increase in mononuclear white blood cells in the longer interval group). Interestingly, platelet counts were reported to be increased after LDGT by an average of 9% and 8% in groups A and B, respectively (both $P < 0.001$). Thrombocytosis is a manifestation of acute rheumatic inflammation.²⁶ If the modest increase in platelets following short term LDGT is truly consistent, one may suspect a possible explanation of decreased platelet margination in microvasculature, analogous to that of neutrophils,¹¹ following glucocorticoid administration. This observation deserves further investigation, particularly with respect to possible glucocorticoid and microvascular functional interactions.²⁵ Also, the finding of significant opposite effects of LDGT on mononuclear white blood cell counts by 2.00 am (decreased) *v* 7.30 am (increased) dosing warrants further attention, as stated by the investigators.¹³

Overall interpretation of short term LDGT effects and timing considerations

Four of the 13 patients in each group received 7.5 mg prednisolone daily, but they did not appear to have better responses than the remainder who received 5 mg with respect to improved morning stiffness, pain at rest, Lansbury index, or decreased IL-6 concentrations (figure 1 in¹³). Also, patients who received the 7.5 mg dose did not have higher baseline concentrations of IL-6 than those who received 5 mg (table 3 in¹³). The accumulated prednisolone dosage over 4 days totalled either 20 mg (18 patients) or 30 mg (eight patients) in this study, which is certainly modest. The outcome results indicate impressive potency of LDGT in suppressing selected disease manifestations of active rheumatoid arthritis, at least over five days in a hospital environment.

The most dramatic findings of this study¹³ are the marked morning clinical responses and decreased serum IL-6 concentrations following four days of LDGT given at 2.00 am. However, these results are intrinsically consistent with data in previous reports. Normally, cortisol levels start to increase at 2.00 am, peak at 8.00 am, and return to baseline by noon.^{12,15} Sequentially, rheumatoid arthritis symptoms usually improve by mid-morning or several hours after awakening and the cortisol peak.²⁷ Interestingly, serum IL-6 concentrations normally peak earlier than ACTH or cortisol, between 1.00 and 4.00 am in normal male volunteers.¹⁴ However, in rheumatoid arthritis patients, this IL-6 peak is phase delayed, occurring between 2.00 am and 7.00 am, and is much higher than normal^{15,16} (figure). In the same rheumatoid arthritis patients,¹⁵ both the ACTH and cortisol curves were slightly phase advanced from normal (figure), suggesting stimulation by IL-6, although their overall secretion remained paradoxically normal. A circadian rhythm of increased stiffness, joint pain at rest, and indices of joint activity in the mornings has been reported in rheumatoid arthritis.²⁷ The marked clinical improvements at 7.30 am, following 2.00 am LDGT administration¹³ may have resulted from the direct effects of exogenous prednisolone in amplifying



A heuristic scheme showing the circadian rhythmicity of plasma ACTH (upper panel), cortisol (middle panel), and interleukin-6 (IL-6) (lower panel) in normal controls (solid lines) and early, untreated patients with rheumatoid arthritis (interrupted lines). Note the early (phase advanced) circadian peaks of ACTH and cortisol in the patients, who have a later (phase delayed) marked peak elevation in their circadian plasma IL-6. The latter cytokine is a potent stimulator of the hypothalamic-pituitary-adrenal axis, which probably drives the phase advanced plasma ACTH and cortisol circadian peaks in the rheumatoid arthritis patients. Paradoxically, the mean plasma ACTH and cortisol concentrations over 24 h are not raised in the patients.¹⁵

and phase advancing the effect of the usual morning glucocorticoid (cortisol) surge¹² on rheumatoid arthritis manifestations.^{10, 27}

Data on rheumatoid arthritis activity during the 24 hours following the fourth and last prednisolone dose in each group were not provided. It is not known if the superior, early phase, type 1 responses found at 7.30 am in group A would have been maintained over the full diurnal period.

Regarding correlations between serum IL-6 levels and activity indicators of rheumatoid arthritis (table), all 26 patients showed significant baseline correlations between the 7.30 am serum IL-6 concentrations and the following: morning stiffness ($r = 0.5, P < 0.01$); C reactive protein ($r = 0.6, P < 0.01$), and SAA protein ($r = 0.6, P < 0.001$). Following LDGT in the 2.00 am administration group (A), the Δ decrements in IL-6 correlated impressively with changes in C reactive protein ($r = 0.74, P < 0.01$) and SAA protein ($r = 0.84, P < 0.001$), but not with clinical improvement. Following LDGT in the 7.30 am administration group (B), the Δ decrements in IL-6 correlated with C reactive protein ($r = 0.62, P < 0.05$) and Ritchie index ($r = 0.67, P < 0.05$), but not with SAA protein. The highly correlated, early phase (but not later phase) decrements of IL-6 and SAA protein in response to LDGT deserve further investigation.

Plasma ACTH and cortisol levels were not assayed in this study.¹³ That information might have allowed more critical interpretation of the complex interactions between HPA axis functions⁸⁻¹¹ and the measured indicators of disease activity in rheumatoid arthritis.

Whether or not the observed efficacy-response patterns to 2.00 am *v* 7.30 am LDGT would have been maintained over a longer period than five days, or if one dosing schedule would have continued to be subjectively more effective than the other, cannot be predicted from the reported short term data.¹³ Neither can one reliably expect that any differences would be found between the dosing schedules in longer term, chronic adverse sequelae of LDGT, in particular osteoporosis.^{2, 3, 5} Importantly, this complication is also influenced by sex steroids⁶ as well as by the effects of androgens in modulating the influences of glucocorticoids⁷ and IL-6²⁸ upon bone mass reduction.

The type 1, early phase (5½ hour) anti-inflammatory responses to LDGT may be due to the dual acute (1×BHL) direct inhibitory actions of glucocorticoids upon the neurogenic-vascular permeability mechanisms^{11, 25, 29} as well as subacute (4+×BHL) anti-inflammatory processes.^{11, 24, 30} Glucocorticoids inhibit the production or actions of various cytokines, for example, TNF α , IL-1, IL-6, IL-12, and others,^{11, 23, 24, 30, 31} which can all influence the inflammatory response. These acute and subacute interactions are complex. Glucocorticoids synergise with IL-6 in stimulation of acute phase proteins,²² which can have anti-inflammatory and wound healing actions.²³ Also, the inflammatory cytokines (TNF α , IL-1, and IL-6), and particularly IL-6, have synergistic roles in HPA axis activation and increasing glucocorticoid secretion,³² a process that appears to be defective in rheumatoid arthritis patients.¹⁵

The dramatic decrease from baseline in the 7.30 am serum IL-6 concentrations in the 2.00 am LDGT group (A) may reflect direct inhibition of this cytokine by the exogenous glucocorticoid.³⁰ Additionally, the lesser decrease in IL-6 concentrations in the 7.30 am LDGT group (B) may reflect indirect effects of glucocorticoid mediated suppression of other cytokines, for example, TNF α and IL-1, or hormones, for example, catecholamines,^{11, 24, 31} that normally stimulate IL-6 synthesis or secretion.^{11, 23}

The early phase, type 1 LDGT responses may be reflecting a domain of mainly physiological interactions, for example, hormonal and neural/capillary functions,^{11, 25, 29} including the important immunoregulatory and modulatory role of nitric oxide (NO) on inflammation.³³ Glucocorticoids inhibit the expression of an inducible (but not the constitutive) nitric oxide synthase (NOS) in vascular endothelial cells.³⁴ The later phase, subacute responses may result from either LDGT suppression of cell mediated processes in inflammation¹¹ or multifactorial low dose pharmacological “add on” therapy effects.²

Optimal management of active rheumatoid arthritis is individualised and usually challenging, without ability to rely upon one or another method of treatment in all patients. Among the options, use of LDGT appears to be

Significant correlations (r) between serum interleukin-6 levels and activity indicators of rheumatoid arthritis at baseline (day 0) and Δ changes after low dose glucocorticoid treatment (LDGT) (day 5) *

Clinical or laboratory features	Baseline (day 0) pre-LDGT (n=26)		Δ changes after LDGT (day 5)			
	r	P value	2.00 am dosing (n=13)		7.30 am dosing (n=13)	
Age	0.38	< 0.05				
Morning stiffness	0.5	< 0.01				
Ritchie Index					0.67	< 0.05
CRP	0.6	< 0.01	0.74	< 0.01	0.62	< 0.05
SAA	0.6	< 0.001	0.84	< 0.001		

* Assessments at 7:30. CRP, C reactive protein; SAA, serum anyloid-A protein

increasing and it is now a major component. However, it is not necessarily a first line approach² or by all means indicated in every case.⁵ Other types of hormonal treatment have been investigated in rheumatoid arthritis, for example, androgens in men³⁵ and postmenopausal women.³⁶ Such an approach may have an intrinsic anti-inflammatory and anabolic value as well as favourably modulating certain adverse catabolic effects of LDGT, for example, osteoporosis.^{6,7,37} Suppression of rheumatoid activity by glucocorticoids as well as androgenic-anabolic steroids is most complex^{29,37} and currently not well defined clinically. Steroid treatment alone may not achieve the long term efficacy and acceptability of current combinational drug regimens for rheumatoid arthritis.³⁸ However, such hormones may serve useful adjunctive roles to current^{2,4,38} and future immunobiological^{39,40} approaches to the treatment of rheumatoid arthritis.

The optimal role of glucocorticoids and androgenic-anabolic hormones in the management of rheumatoid arthritis requires further critical study. Issues of dosage and timing raised by the study of Arvidson *et al*¹³ are among the many challenging questions that need to be addressed. For the present, physicians employing LDGT in rheumatoid arthritis are encouraged to review the relevant issues critically when making individual patient decisions, based upon their clinical acumen, experienced judgments, and the available research data.

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- 1 West HF. Rheumatoid arthritis: the relevance of clinical knowledge to research activities. *Abstracts World Med* 1967;41:401-17.
- 2 Masi AT. Low dose glucocorticoid therapy in rheumatoid arthritis (RA): transitional or selected add on therapy? *J Rheumatol* 1983;10:675-8.
- 3 Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term, corticosteroid therapy in rheumatoid arthritis: An analysis of serious adverse events. *Am J Med* 1994;96:115-23.
- 4 Kirwan JR, the Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. *N Engl J Med* 1995;333:142-6.
- 5 Morrison E, Capell H. Corticosteroids in the management of rheumatoid arthritis. *Br J Rheumatol* 1996;35:2-4.
- 6 Slemenda C, Longcope C, Peacock M, Hui S, Johnston CC. Sex steroids, bone mass, and bone loss: a prospective study of pre-, peri-, and postmenopausal women. *J Clin Invest* 1996;97:14-21.
- 7 Reid IR, Wattie DJ, Evans MC, Stapleton JP. Testosterone therapy in glucocorticoid-treated men. *Arch Intern Med* 1996;156:1173-7.
- 8 Masi AT, Chrousos GP. Hypothalamic-pituitary-adrenal-glucocorticoid axis function in rheumatoid arthritis. *J Rheumatol* 1996;23:577-81.
- 9 Gudbjörnsson B, Skogseid B, Öberg K, Wide L, Hällgren R. Intact adrenocorticotropic hormone secretion but impaired cortisol response in patients with active rheumatoid arthritis. Effect of glucocorticoids. *J Rheumatol* 1996;23:596-602.
- 10 Neeck G, Federlin K, Graef V, Rusch D, Schmidt KL. Adrenal secretion of cortisol in patients with rheumatoid arthritis. *J Rheumatol* 1990;17:24-9.
- 11 Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med* 1995;332:1351-62.
- 12 Orth DN, Kovacs WJ, Debold CR. The adrenal cortex. In: Wilson JD, Foster DW, eds. *Williams textbook of endocrinology*, 8th ed. Philadelphia: WB Saunders, 1992;489-611.
- 13 Arvidson NG, Gudbjörnsson B, Larsson A, Hällgren R. The timing of glucocorticoid administration in rheumatoid arthritis. *Ann Rheum Dis* 1996;55.
- 14 Sothorn RB, Roitman-Johnson B, Kanabrocki EL, Yager JG, Roodell MM, Weatherbee KS, et al. Circadian characteristics of circulating interleukin-6 in men. *J Allergy Clin Immunol* 1995;95:1029-35.
- 15 Crofford LJ, Kalogeras KT, Mastorakos G, Magiakou M-A, Wells J, Kanik KS, et al. Circadian relationships between interleukin (IL)-6 and hypothalamic-pituitary-adrenal axis hormones: failure of IL-6 to cause sustained hypercortisolism in patients with early untreated rheumatoid arthritis. *J Clin Endocrinol Metab* (in press).
- 16 Arvidson NG, Gudbjörnsson B, Rydén A-C, Elfman L, Tötterman TH, Hällgren R. Circadian rhythm of serum interleukin-6 in rheumatoid arthritis. *Ann Rheum Dis* 1994;53:521-4.
- 17 Pickup ME. Clinical pharmacokinetics of prednisone and prednisolone. *Clin Pharmacokinet* 1978;4:111-28.
- 18 Meikle AW, Tyler FH. Potency and duration of action of glucocorticoids. Effects of hydrocortisone, prednisolone and dexamethasone on human pituitary-adrenal function. *Am J Med* 1977;63:200-7.
- 19 Mihara M, Moriya Y, Kishimoto T, Ohsugi Y. Interleukin-6 (IL-6) induces the proliferation of synovial fibroblastic cells in the presence of soluble IL-6 receptor. *Br J Rheumatol* 1995;34:321-5.
- 20 Schindler R, Mancilla J, Endres S, Ghorbani R, Clark SC, Dinarello CA. Correlations and interaction in the production of interleukin-6 (IL-6), IL-1 and tumor necrosis factor (TNF) in human blood mononuclear cells: IL-6 suppresses IL-1 and TNF. *Blood* 1990;75:40-7.
- 21 Tilg H, Trehu E, Atkins MB, Dinarello CA. Interleukin-6 (IL-6) as an anti-inflammatory cytokine: induction of circulating IL-1 receptor antagonist and soluble tumor necrosis factor receptor p55. *Blood* 1994;83:113-8.
- 22 Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. *Biochem J* 1990;265:621-36.
- 23 Akira S, Taga T, Kishimoto T. Interleukin 6 in biology and medicine. *Adv Immunol* 1993;54:1-78.
- 24 Fahey JV, Gutre PM, Munck A. Mechanisms of anti-inflammatory actions of glucocorticoids. *Adv Infl Res* 1981;2:21-51.
- 25 Miura T, Inagaki N, Yoshida K, Nakajima T, Nagai H, Koda A. Mechanisms for glucocorticoid inhibition of immediate hypersensitivity reactions in rats. *Jpn J Pharmacol* 1992;59:77-87.
- 26 Benedetti FDE, Robbioni MM, Viola S, Albani S, Martini A. Serum interleukin-6 levels and joint involvement in polyarticular and pauciarticular juvenile arthritis. *Clin Exp Rheum* 1992;10:493-8.
- 27 Harkness JAL, Richter MB, Panayi GS, van de Pette K, Unger A, Pownall R, et al. Circadian variation in disease activity in rheumatoid arthritis. *BMJ* 1982;284:551-4.
- 28 Bellido T, Jilka RL, Boyce BF, Girasole G, Broxmeyer H, Dalrymple SA, et al. Regulation of interleukin-6, osteoclastogenesis, and bone mass by androgens: the role of the androgen receptor. *J Clin Invest* 1995;95:2886-95.
- 29 Masi AT, Feigenbaum SL, Chatterton RT, Cutolo M. Integrated hormonal-immunological-vascular (H-I-V triad) systems interactions in rheumatic diseases. *Clin Exp Rheumatol* 1995;13:203-16.
- 30 Zanker B, Walz G, Wieder KJ, Strom TB. Evidence that glucocorticoids block expression of the human interleukin-6 gene by accessory cells. *Transplantation* 1990;49:183-5.
- 31 Elenkov IJ, Papanicolaou DA, Wilder RL, Chrousos GP. Modulatory effects of glucocorticoids and catecholamines on human interleukin-12 and interleukin-10 production: clinical implications. *Proc Assoc Am Physicians* 1996;108:374-81.
- 32 Perlstein RS, Whitnall MH, Abrams JS, Mougey EH, Neta R. Synergistic roles of interleukin-6, interleukin-1, and tumor necrosis factor in the adrenocorticotropic response to bacterial lipopolysaccharide in vivo. *Endocrinology* 1993;132:946-52.
- 33 Farrell AJ, Blake DR. Nitric oxide. *Ann Rheum Dis* 1996;55:7-20.
- 34 Radomski MW, Palmer RMJ, Moncada S. Glucocorticoids inhibit the expression of an inducible, but not the constitutive, nitric oxide synthase in vascular endothelial cells. *Proc Natl Acad Sci USA* 1990;87:10043-7.
- 35 Cutolo M, Balleari E, Giusti M, Intra E, Accardo S. Androgen replacement therapy in male patients with rheumatoid arthritis. *Arthritis Rheum* 1991;34:1-5.
- 36 Booijs A, Biewenga-Booijs CM, Huber-Bruning O, Cornelis C, Jacobs JWJ, Bijlsma JWJ. Androgens as adjuvant treatment in postmenopausal female patients with rheumatoid arthritis. *Ann Rheum Dis* 1996;55:1-5.
- 37 Masi AT, DaSilva JAP, Cutolo M. Perturbations of hypothalamic-pituitary-gonadal (HPG) axis and adrenal androgen (AA) functions in rheumatoid arthritis. *Bailliere's Clin Rheum* 1996;10:295-332.
- 38 O'Dell JR, Haire CE, Erikson N, Drymalski W, Palmer W, Eckhoff PJ, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996;334:1287-91.
- 39 Bresnihan B, Lookabaugh J, Witt K, Musikie P. Treatment with recombinant human interleukin-1 receptor antagonist in rheumatoid arthritis: results of a randomized double-blind, placebo-controlled multicenter trial. *Arthritis Rheum* 1996;39:S73.
- 40 Baumgartner S, Moreland LW, Schiff MH, Tindall E, Fleischman RM, Weaver A, et al. Double-blind, placebo-controlled trial of tumor necrosis factor receptor (p80) fusion protein (TNFR:Fc) in active rheumatoid arthritis. *Arthritis Rheum* 1996;39:S73.