GLUCOCORTICOIDS IN EARLY RHEUMATOID ARTHRITIS

Cover front : "Two bridges over East River" door Raoul Dufy
met toestemming van Merck Sharp & Dohme

Lay-out : Haaring Automatisering, Scherpenzeel

Drukwerk : Drukkerij Haasbeek, Alphen a/d Rijn

ISBN : 90 71736 28 8

Uitgeverij : Belvédère/Medidact, Overveen/Alphen aan den Rijn

Het in dit proefschrift beschreven onderzoek werd mogelijk gemaakt door een subsidie van het Nationaal Reumafonds.

GLUCOCORTICOIDS IN EARLY RHEUMATOID ARTHRITIS

Glucocorticoiden bij vroege reumatoide artritis

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de Rector Magnificus, Prof. Dr. W.H. Gispen,
ingevolge het besluit van het College voor Promoties
in het openbaar te verdedigen op
vrijdag 4 oktober 2002 des namiddags te 12.45 uur

door

Amalia A van Everdingen

geboren 21 juni 1947 te Dordrecht

Promotor : Prof Dr JWJ Bijlsma
afdeling Reumatologie en Klinische Immunologie
Universitair Medisch Centrum Utrecht

Co-promotor : Dr JWG Jacobs
afdeling Reumatologie en Klinische Immunologie
Universitair Medisch Centrum Utrecht

De publicatie van dit proefschrift werd mede mogelijk gemaakt met de financiële steun van Merck Sharp & Dohme, het Nationaal Reumafonds, Aventis Pharma, Boehringer Ingelheim, Byk Nederland, Schering-Plough, Eli Lilly Nederland, Wyeth, Amgen en Novartis Pharma.

CONTENTS

Introduction, Rationale and Outline of the Thesis

CHAPTER 1

INTRODUCTION*

Rheumatoid Arthritis (RA)

Treatment of RA

RA is a chronic inflammatory systemic disease, mainly characterised by synovitis of small joints, especially of hands and feet.[1] Persistent synovitis leads to pain, joint swelling, stiffness, decreased mobility and joint space narrowing; synovial hyperplasia causes erosions and joint deformities.[2] Extra-articular as well as systemic features may occur.[1] Pain, loss of physical functioning, fatigue and other symptoms of RA have a major impact on social life. The disease is costly to individuals, families and society in both economic and social terms.

The aetiology of RA is still incompletely known; a multiplicity of genetic, environmental, immunologic and psychoneuroendocrine factors like dysfunction of the hypothalamic-pituitary-adrenal (HPA-) axis plays a role.[3-5] An initial infectious event could be involved but there is no convincing evidence for this hypothesis.[1] Irreversible joint damage of patients with RA often starts within the first two years of the disease.[2, 6-9] Joint damage in RA consists on the one hand of cartilage thinning with joint space narrowing and on the other hand of erosions as a characteristic feature of bone destruction. In the pathogenesis of joint damage, T-cells and macrophages and their products in the hyperplastic rheumatoid synovial lining layer play a major role. T-cells and macrophages produce cytokines as interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α) that drive the inflammatory and destructive processes in RA. In addition, macrophages and fibroblasts produce proteolytic enzymes such as matrix metalloproteinases (MMPs), which are thought to be of particular importance in the development of joint erosions.[10]

Treatment of RA

Patients with RA are best treated by a rheumatologist participating in a multidisciplinary team of specialised health professionals, including a physical therapist, occupational therapist, nurse practitioner in rheumatology and a medical (psycho-) social worker. Orthopedic and reconstructive surgery can play an important role in relieving pain and in restoring or maintaining physical function. Guarded intensive physical training in groups is a recently developed additional strategy.[11]

* Part of this introduction has been published [15, 46, 47]

Drug treatment of RA usually consists of a combination of a non-steroidal anti-inflammatory drug (NSAID) and a disease-modifying anti-rheumatic drug (DMARD), for instance hydroxychloroquine, sulphasalazine, methotrexate, ciclosporin, leflunomide or a combination of DMARDs. New biological agents, such as tumor necrosis factor (TNF)-alpha blockers and interleukin-1 (IL-1) receptor antagonists, are promising.[12, 13] Glucocorticoids (GC) have a special place in the treatment of RA and will be discussed in detail, as they are the focus of this thesis.

Glucocorticoids in RA

GC are widely used in the treatment of patients with RA since the initial report by Hench et al. that cortisone dramatically ameliorated the symptoms of RA.[14] A period of enthusiasm in the fifties about the effects of GC was followed by a long period of cautious application of GC for RA, because of the many side effects. Despite the continuing debate about the risks and benefits GC are considered by many patients with RA, as well as by their physicians, to be most effective symptomatic drugs, and their anti-inflammatory properties are well established. New insights in the mechanism of GC, especially their effects on the immune system and the hypothalamic pituitary adrenal (HPA) axis, have provided justification for discretionary use of these drugs in RA.[15-17] Fundamental research continues to unravel the complexity of the biological effects of GC, such as on gene transcription, and careful clinical observations refine their therapeutic use.[18]

The role of the glucocorticoid receptor (GR) in RA

The HPA-axis plays a crucial role in the homeostasis of the human body, including regulation of inflammation. GC have potent anti-inflammatory actions through their influence on the HPA- axis and the stress response. In this way, GC influence nearly all cells and organ systems.[15] GC exert their effects through the GC receptor (GR) located in the cytoplasm of target cells at low doses.[16] At higher doses, genomic (i.e. through the GR) as well as non-genomic modes of action play a role. [19] Schlaghecke et al. showed a diminished GR-number (sites/cell) in peripheral blood mononuclear leucocytes (PBMC) of RA patients with active disease of longer duration (mean 6 years) compared to healthy controls.[20] In contrast, Sanden et al. showed an increase in the number of GRs in patients with a large range of disease activity compared to healthy controls. This increased number decreased on GC therapy in a dose dependent way.[21]

In daily clinical practice, not all patients do respond in the same way to GC treatment: some do not respond at all, others do at low doses, while others require

larger doses for seemingly identical clinical situations. In a study of lupus patients with nephrotic syndrome treated with GC, a distinct effect of GR level was observed on the clinical responsiveness to GC therapy.[22] Steroid resistant asthma patients show abnormalities of GR-expression.[23] So, the GR number of PBMC might be helpful to predict which RA patients will respond to low dose prednisone and which patients need higher doses.

Clinical data on GC in RA

In daily practice, GC seem to have greatest effect on morning stiffness and other systemic symptoms, such as fatigue, weakness and anorexia. An increase in haemoglobin concentration is noted, together with a decrease in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Walking time and grip strength of the hands often increase. Joint inflammation is more variably influenced. In cases of extra-articular disease, such as pericarditis and pleuritis, GC are effective, but often medium to high dosages are necessary to control these complications. At present, the use of long-term treatment with low-dose GC in clinical practice is different from country to country and estimated to range from 25 up till 75% of patients with longstanding RA.[24, 25] Nevertheless, this use of oral low-dose GC in the treatment of RA gives rise to continued debate. Low-dose GC (prednisone $\leq$ 7.5 mg/day) effectively and rapidly suppress signs and symptoms of inflammation in RA, but adverse effects limit their role.[25] In the opinion of most physicians and patients, the beneficial effects of low-dose GC seem to outweigh their adverse effects.[26]

Clinical studies on GC in RA

Numerous short-term studies have demonstrated the ability of low-doses of GC to partly suppress the signs and symptoms of inflammation of patients with active RA. Only a limited number of studies has evaluated the effect of these agents versus placebo or NSAIDs for more than 3 months.[16] In 1996 a systemic review and a meta-analysis of the effectiveness of low-dose GC for the treatment of RA were published.[27] Only 9 studies were identified that fulfilled the set criteria: randomised, controlled, parallel or crossover trials lasting 3 months or longer using GC at a mean dosage of less than or equal to 15 mg/daily. Four were placebo-controlled and the other 5 were active drug-controlled studies comparing the effect of prednisone with that of another agent. Outcome measures included the number of tender and swollen joints and ESR. From the multiple publications of the Empire Rheumatism Council and the Joint Commission of the Medical Research Council

and Nuffield Foundation, one study was included comparing the effects of cortisone with those of aspirin and one comparing the effect of prednisone with that of aspirin.[28, 29] From these meta-analyses it is suggested that GC appear to be more effective than placebo and are nearly equivalent to traditional DMARDs in improving most of the conventional outcome measures. However, data were limited; the treatment episodes were relatively short (7 months on average) and the GC were given late in course of the disease and often in combination with DMARDs.

So, the widespread use of low-dose GC in RA is still based on a rather low number of controlled studies. However, they generally uphold the widely held belief that low-dose GC are effective in the treatment of RA.[2] Until recently almost all studies with GC treatment are conducted in patients with RA of longer duration (mostly more than several years). In the past few years studies were performed among patients with early RA.

Joint protective properties of GC in RA

The review by Weiss in 1989 of GC treatment in RA, in which disease modifying properties were addressed, was followed by renewed clinical and scientific interest in these drugs, especially since potential serious adverse and side effects of GC therapy are more easily managed nowadays.[30,31]

In 1995 Kirwan demonstrated a significant reduction in progression of radiologically detected joint damage of the hands, if GC were added to antirheumatic treatment in a double-blind placebo-controlled study among 128 patients with early RA.[8] Patients received prednisone (7.5 mg daily) or placebo for 2 years in addition to NSAIDs (95% of patients) and DMARDs (71% of patients). After 2 years both the mean total number of erosions and the number of patients with erosions were significantly lower in the GC group. Improvement in clinical parameters was found only during the first year of therapy. It was concluded that a fixed daily dose of 7.5 mg given as adjuvant therapy for early active RA retards radiological progression of joint destruction. However, only hands were evaluated for the radiological score. In the follow-up study of the same patients joint destruction resumed at the previous rate at a lower level after tapering and discontinuation of prednisone.[32]

Zeidler et al. performed a study in 192 patients with early RA. In this double-blind placebo-controlled trial of patients treated with gold sodium thiomalate or methotrexate, the effect of 5 mg daily of adjuvant prednisolone therapy was evaluated.[33] Prednisolone proved to be effective in further reducing inflammatory symptoms as well as radiological progression of erosions, confirming the data of

Kirwan et al. In the COBRA study of early RA, Boers et al. compared the effect of a combined step-down strategy with prednisone, methotrexate and sulphasalazine with that of sulphasalazine monotherapy.[34] The combined therapeutic regimen with prednisone (initially 60mg/day, tapered every 6 weeks to 7.5 mg/day and stopped at week 28) slowed down radiological damage significantly more than sulphasalazine alone at weeks 28, 56 and 80. Patients in the prednisone group also showed rapid disease control as measured by tender joint count, grip strength, overall assessment by the independent assessor on a 100 mm visual analogue scale, McMaster Toronto arthritis questionnaire, and ESR. After stopping the prednisone treatment at 26 weeks, these indices became comparable with those of the sulphasalazine only group. Other studies in RA patients, comparing effects of treatment with sulphasalazine, methotrexate or a combination of both, did not show such significant differences in effect between these therapeutic regimens in retardation of radiologically detected joint damage suggesting that the joint-sparing effect in the study of Boers is based on the GC-therapy.[35, 36] The follow-up COBRA study showed sustained suppression of the rate of radiological progression in patients with early RA, independent of subsequent antirheumatic therapy in contrast to the study of Kirwan.[37] So, several studies suggest that prednisone is the potent inhibitor of joint damage.

Effects of GC on general wellbeing of RA patients

There are indications for dysfunction of the HPA axis at the hypothalamic level in RA.[4, 5] Due to this, the stress response may be influenced, modifying the autonomic system and behavioural adaptation.[15, 38] In several studies of patients with RA, treated with GC, parameters such as pain and physical ability ameliorated.[8, 32, 39] In one study with short term high-dose GC treatment of patients with active RA a positive effect on disease activity, physical ability, psychological and social functioning as well as the impact on daily life was described.[40]

However, relatively little is known about the long-term effects of GC on parameters of wellbeing.[41]

Adverse and Side Effects of GC (also Table 1.)

Given the diversity of their mechanisms and sites of action, it is not surprising that GC can cause a wide array of adverse and side effects, some of which cannot be completely avoided. Theoretically, the risk for most of these complications is dosage and time-dependent. It is a striking clinical observation that some patients develop

TABLE 1

Adverse effects of GC therapy [46]

Onset early in therapy
Emotional lability, Insomnia
Enhanced appetite, weight gain
Enhanced in patients with genetic predisposition such as diabetes mellitus and underlying risk factors or concomitant use of other drugs
Acne vulgaris
Diabetes mellitus
Hypertension
Peptic ulcer disease
When supraphysiologic GC treatment is sustained
Cushingoid appearance
Hypothalamic-pituitary-adrenal suppression, adrenal insufficiency
Impaired wound healing
Myopathy, muscular atrophy, skin atrophy
Osteonecrosis
Immunosuppression, Predisposition to infections
Glaucoma
Delayed and insidious, probably dependent on cumulative doses
Atherosclerosis
Cataract
Steatosis hepatis
Growth retardation in children
Loss of scalp hair and (more often) thinning of scalp hair
Skin atrophy with easy bruisability of skin
Osteoporosis
Less frequent or less predictable
Pancreatitis
Pseudotumor cerebri
Psychosis

severe adverse effects with relatively small doses of GC, while other patients receive rather high doses without obvious serious adverse effects. This apparent individual susceptibility for adverse effects does not seem to parallel the individual's susceptibility for beneficial effects.

The toxicity of prednisone of 15 mg or less for at least 1 year in the treatment of RA has been evaluated.[42] Although disease severity is an important confounding factor in interpreting this evaluation, 3 serious (groups of) adverse events were identified that caused substantial morbidity: gastrointestinal ulcers and/or bleeding or ulcers, infections and osteopenia/osteoporosis.

RATIONALE OF THE THESIS

In recent years, therapeutic approaches of patients with RA are aimed at more early phases of the disease in order to reduce or prevent joint damage.[43-45] In daily practice, GC are widely used in combination with disease-modifying drugs to diminish disease activity and to relief symptoms.[26] Because of adverse and side effects, courses with GC therapy are generally short with the lowest possible dosis. Recent studies with combination therapies support the hypothesis that GC in itself have disease-modifying properties.[27-29, 32]

To investigate the disease-modifying properties of GC, without interference of DMARDs, we performed a double-blind, placebo controlled, 2-year study (and 1 year follow-up) with low-dose GC as monotherapy in DMARD naive patients with early active RA, in contrast to other studies where GC were added to DMARDs. The results of this study with focus on retardation of joint damage in relation to parameters of disease activity and side effects will be addressed in **Chapter 2**.[46]

We assessed in our study in more detail the effects of low-dose GC therapy of patients with early RA on bone and fracture rate (**Chapter 3**).

The effects of GC on wellbeing in patients with early RA were investigated and the role of the use of additional therapies in assessing parameters of wellbeing was also evaluated (**Chapter 4**).

In literature a diminished GR number was described in patients with RA of longer duration. This could especially be present in patients with early-diagnosed RA. To investigate the hypothesis that GR-downregulation might play a role in the etiopathogenesis of RA as a result of impairment of the HPA-axis, we compared the GR-expression as well as the serum cortisol levels of early RA patients with those of sex-and age-matched healthy controls (**Chapter 5**).

To investigate the hypothesis that early RA patients with a higher GR-number might respond better clinically to low dose prednisone than patients with a lower GR-number, we investigated whether there was a relation between the GR-number in peripheral blood mononuclear cells (PBMC) determined at baseline in patients with early RA treated with 10 mg prednisone and the clinical effect of the prednisone therapy during the 2 years of treatment (**Chapter 6**).

REFERENCES

1. Harris ED jr. Clinical Features of Rheumatoid Arthritis. In: Kelley WN. Ruddy S, Harris ED Jr and Sledge CB, Eds. Textbook of Rheumatology (6e ed). Philadelphia, WB Saunders 2000;65:967-1000.
2. Kirwan JR. Conceptual issues in scoring radiographic progression in rheumatoid arthritis. J Rheumatol 1999;26:720-5.
3. Bijlsma JWJ, Cutolo M, Masi AT, et al. The neuroendocrine immune basis of rheumatic diseases. Immunol Today 1999;20:298.
4. Schlaghecke R, Kornely E, Wollenhaupt J, et al. Glucocorticoid receptors in rheumatoid arthritis. Arthritis Rheum 1992;35:1281-8.
5. Straub RH, Cutolo M. Involvement of the hypothalamic-pituitary-adrenal/gonadal axis and the peripheral nervous system in rheumatoid: viewpoint based on a systemic pathogenesic role. Arthritis Rheum 2001;44:493-507.
6. Hulsmans HM, Jacobs JWG, van der Heijde DM, et al. The course of radiologic damage during the first six years of rheumatoid arthritis. Arthritis Rheum 2000;43:1927-40.
7. Heijde DMFM van der, Riel PLCM van, Nuver-Zwart HH, Gribnau FW, Putte LBA van de. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989;1:1036-8.
8. Kirwan JR. Arthritis and Rheumatism Council Low-dose Glucocorticoid study Group: The effect of glucocorticoid on joint destruction in RA. N Engl J Med 1995;333: 142-6.
9. Tugwell P, Boers M. Long acting drug combinations in rheumatoid arthritis, updated overview. In: Wolfe F, Pincus T (Eds). Rheumatoid arthritis: pathogenesis, assessment, outcome and treatment. New York: Marcel Dekker 1994;357-71.
10. Cunnane G, FitzGerald O, Hummel KM, et al. Synovial tissue protease gene expression and joint erosions in early rheumatoid arthritis. Arthritis Rheum 2001;44 :1744-53.
11. Jong Z de, Munneke M, Jansen A, et al. A long-term high intensity exercise program (RAPIT) is effective in rheumatoid arthritis (RA) patients without additional joint damage or disease exacerbation: a randomized controlled trial. Arthritis Rheum 2001;44:S380
12. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41: 1552-63.

13. Bresnihan B, Alvaro-Garcia JM, Cobby M, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 1998;41:2196-204.
14. Hench PS, Kendall EC, Slocumb CH, et al. Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions: a study in clinical physiology. Arch Intern Med 1950;85:546-66.
15. Bijlsma JWJ, Everdingen AA van, Jacobs JWG. Corticosteroids in rheumatoid arthritis: how best to use them? Clin Immunother 1995;3:271-86.
16. Da Silva JAP, Bijlsma JWJ. Optimizing glucocorticoid therapy in rheumatoid arthritis. Rheum Dis Clin North Am 2000;26:859-80.
17. Bijlsma JWJ, Straub RH, Masi AT, et al. Neuroendocrine immune mechanisms in rheumatic diseases. Trends in Immunology 2002;23:59-6.
18. Kimberly RP. Glucocorticoids. Curr Opin Rheumatol 1994;6:273-80.
19. Buttgereit F, Wehling M, Burmester GR. New hypothesis of modular glucocorticoid actions. Steroid treatment of rheumatic diseases revisited. Arthritis Rheum 1998;41:761-7
20. Schlaghecke R, Beuscher D, Kornely E, et al. Effects of glucocorticoids in rheumatoid arthritis. Diminished glucocorticoid receptors do not result in glucocorticoid resistance. Arthritis Rheum 1994;37:1127-31.
21. Sanden S, Tripmacher R, Weltrich R, et al. Glucocorticoid dose dependent downregulation of glucocorticoid receptors in patients with rheumatic diseases. J Rheumatol 2000;27: 1265-70.
22. Tanaka H, Akama H, Ichikawa Y, et al. Glucocorticoid receptors in normal leucocytes: effects of age, gender, season and plasma cortisol concentrations. Clin Chem 1991;37:1715-19.
23. Sher ER, Leung DY, Surs W, et al. Steroid resistant asthma. Cellular mechanisms contributing to inadequate response to glucocorticoid therapy. J Clin Invest 1994;93:33-9.
24. Pincus T, Marcum SB, Callahan LF. Long-term drug therapy for rheumatoid arthritis in seven rheumatology private practices: 2. Second-line drugs and prednisone. J Rheumatol 1992;19:1885-94.
25. Caldwell JR, Furst DE. The efficacy and safety of low-dose corticosteroids for rheumatoid arthritis. Semin Arthritis Rheum 1991;21:1-11.
26. Byron MA, Mowat AG. Corticosteroid prescribing in RA: the fiction and the fact. Br J Rheumatol 1985;24:164-8.

27. Saag KG, Criswell LA, Sems KM, et al. Low-dose corticosteroids in rheumatoid arthritis: A meta-analysis of their moderate-term effectiveness. Arthritis Rheum 1996;39:1818.
28. Empire Rheumatism Council Sub-Committee: Multi-center controlled trial comparing cortisone acetate and acetyl salicylic acid in the long-term treatment of rheumatoid arthritis. Ann Rheum Dis 1955;14:353-63.
29. Joint Committee of the Medical Research Council and Nuffield Foundation on Clinical Trials of Cortisone, ACTH, and Other Therapeutic Measures in Chronic Rheumatic Diseases: A comparison of prednisone with aspirin or other analgesics in the treatment of rheumatoid arthritis. Ann Rheum Dis 1959;18:173-87.
30. Weiss MM. Corticosteroids in rheumatoid arthritis. Semin Arthritis Rheum 1989;19:9-21.
31. Bijlsma JWJ. Long-term glucocorticoid treatment of rheumatoid arthritis: risk or benefit? Rheumatol Eur 1998;27:67-9.
32. Hickling P, Jacoby RK, Kirwan JR and the Arthritis and Rheumatism Council Low Dose Glucocorticoid Study Group. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. Br J Rheumatol 1998;37:930-6.
33. Zeidler H, Rau R, Alkalay I, et al: Efficacy and safety of low-dose prednisolone in early rheumatoid arthritis. Arthritis Rheum 1999;42(Suppl):271 (Abstract).
34. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309-18.
35. Haagsma CJ, Riel PCLM van, Jong AJ de, Putte LBJ van de. Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomised, controlled, double-blind 52 week clinical trial. Br J Rheumatol 1997;36:1082-8.
36. Dougados M, Combe B, Cantagrel A, et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double-blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. Ann Rheum Dis 1999;58:220-5.
37. Landewé RBM, Boers M, Verhoeven AC, et al. COBRA Combination therapy in patients with early rheumatoid arthritis. Long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46:347-56.
38. Bijlsma JWJ, Cutolo M, Masi AT, Chikanza IC. The neuroendocrine immune basis of rheumatic diseases. Immunol Today 1999;20:298-301.

39. Leeuwen MA van, Heijde DM van der, Rijswijk MH, et al. Interrelationship of outcome measures and process variables in early rheumatoid arthritis. A comparison of radiologic damage, physical disability, joint counts and acute phase reactants. J Rheumatol 1994;21:425-9.
40. Jacobs JWG, Geenen R, Evers AWM, et al. Short term effects of corticosteroid pulse treatment on disease activity and the wellbeing of patients with active rheumatoid arthritis. Ann Rheum Dis 2001;60:61-4.
41. Heide A van der, Jacobs JWG, Dinant HJ, Bijlsma JWJ. The impact of endpoint measures in rheumatoid arthritis clinical trials. Semin Arthritis Rheum 1992;21: 287-94.
42. Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse effects. Am J Med 1994;96: 115-23.
43. Heide A van der, Jacobs JWG, Bijlsma JWJ, et al. The effectiveness of early treatment with (second -line) antirheumatic drugs, a randomised controlled trial. Ann Intern Med 1996;124:699-707.
44. Harris Ed Jr. Treatment of rheumatoid arthritis. In: Kelley WN, Harris ED, Ruddy S, Sledge CB, Eds. Textbook of Rheumatology (6e ed). Philadelphia, WB Saunders 2000;66:1001-22.
45. Wilske KR, Healy LA. Remodelling the pyramid-concept whose time has come. J Rheumatol 1989;16:565-7.
46. Everdingen AA van, Jacobs JWG, Siewertsz van Reesema DR, Bijlsma JWJ. Low-dose therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease modifying properties and side effects. A double-blind placebo-controlled trial. Ann Intern Med 2002;136:1-12.
47. Bijlsma JWJ, Everdingen AA van, Huisman AM, et al. Glucocorticoids in rheumatoid arthritis. Effects on erosions and bone. Ann N Y Acad Sci 2002;966:1-9.

Low-Dose Prednisone Therapy for Patients with Early Active Rheumatoid Arthritis: Clinical Efficacy, Disease-Modifying Properties, and Side Effects

CHAPTER 2

AA van Everdingen
JWG Jacobs
DR Siewertsz van Reesema
JWJ Bijlsma

Annals of Internal Medicine 2002
Volume 136:number 1

Abstract

Background

Oral glucocorticoids combined with disease-modifying antirheumatic drugs are beneficial and retard radiologic joint damage in rheumatoid arthritis.

Objective

To investigate the clinical efficacy, disease-modifying properties and side effects of low-dose glucocorticoids as monotherapy for previously untreated patients with early active rheumatoid arthritis.

Design

2-year randomized, double-blind, placebo-controlled clinical trial.

Setting

2 outpatient rheumatology clinics.

Patients

81 patients with early active rheumatoid arthritis who had not been treated with disease-modifying antirheumatic drugs.

Intervention

41 patients were assigned to 10 mg of oral prednisone per day, and 40 were assigned to placebo. Nonsteroidal anti-inflammatory drugs were allowed in both groups. After 6 months, sulfasalazine (2 g/d) could be prescribed as rescue medication.

Measurements

Clinical variables were assessed at baseline and every 3 months; radiologic studies were performed every 6 months. Adverse effects were documented every 3 months.

Results

In the first 6 months, the prednisone group showed more clinical improvement than the placebo group. This effect was not seen after 6 months except in grip strength and the 28-joint score for tenderness. Use of additional therapies was significantly less common in the prednisone group, particularly in the first 6 months. More than 65% of those who completed the study were not taking sulfasalazine.

After month 6, radiologic scores showed significantly less progression in the prednisone group than in the placebo group. No clinically relevant adverse effects were observed, except for a higher incidence of osteoporotic fractures in the prednisone group.

Conclusions

Prednisone, 10 mg/d, provides clinical benefit, particularly in the first 6 months, and substantially inhibits progression of radiologic joint damage in patients with early active rheumatoid arthritis and no previous treatment with disease-modifying antirheumatic drugs. Because of their limited disease-modifying effects, glucocorticoids should be combined with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis.

INTRODUCTION

Drug treatment for rheumatoid arthritis usually consists of a combination of a nonsteroidal anti-inflammatory drug (NSAID) and a disease-modifying antirheumatic drug (for example, sulfasalazine, methotrexate, gold salt, or a combination). New biological agents, such as tumor necrosis factor-α blocking agents and interleukin-1 receptor antagonists, appear promising.[1,2] Glucocorticoids have had a special place in the treatment of rheumatoid arthritis since the publication of the report by Hench and coworkers showing that cortisone dramatically alleviated the symptoms of rheumatoid arthritis by inhibiting inflammation.[3] This period of enthusiasm in the 1950s was followed by a long period in which glucocorticoids were applied cautiously for rheumatoid arthritis because of their many side effects and the recognition that inhibition of inflammation is not necessarily associated with retardation of joint damage.[4]

Ongoing research on glucocorticoids in rheumatoid arthritis focused on both inflammation and joint damage. Some recent studies showed that glucocorticoids reduced the progression of joint damage when added to therapy with disease-modifying antirheumatic drugs. These findings suggested that glucocorticoids might also have disease-modifying properties. If this could be confirmed, glucocorticoids might be used more often, especially since potential serious adverse effects of glucocorticoid therapy are more easily managed today.[5] Secondary osteoporosis is inhibited by potent bisphosphonates, and gastro-intestinal complications of glucocorticoid therapy, especially in combination with NSAIDs, can be reduced by misoprostol, proton-pump inhibitors, or cyclo-oxygenase-2 selective NSAIDs. As yet, disease-modifying properties of low-dose glucocorticoids as monotherapy for patients with early rheumatoid arthritis have not been investigated. The aim of our study was to investigate the clinical efficacy, disease-modifying properties, and side effects of low-dose glucocorticoids as monotherapy for previously untreated patients with early active rheumatoid arthritis.

METHODS

Patients

From October 1992 through October 1995, all consecutive outpatients at the rheumatology departments of the Deventer and Zutphen Hospitals, the Netherlands, who were at least 18 years of age and had early previously untreated rheumatoid arthritis (disease duration < 1 year) that satisfied classification criteria were invited to participate in the study.[6] To be included, patients had to have active disease,

which was defined as the presence of at least two of the following three criteria: 1) early-morning stiffness lasting 30 minutes or longer, 2) 28-joint score for tenderness and 28-joint score for swelling of 3 or more, and 3) Westergren erythrocyte sedimentation rate of 28 mm or higher after 1 hour.[7,8] Exclusion criteria were contraindications to prednisone or NSAIDs, active gastrointestinal problems, serious complicating diseases, severe hypertension, hemorrhagic diathesis, treatment with cytotoxic or immunosuppressive drugs, alcohol or drug abuse, and psychiatric or mental problems. Informed consent was obtained from all patients before participation. Of the 118 eligible patients, 37 declined to participate (**Figure 1**).

Intervention

Pharmacy personnel at Deventer Hospital used a computer-generated randomization procedure to randomly assign the 81 participating patients, in blocks of 10, to one of two treatment groups. One group received two tablets of prednisone, 5 mg, once daily at breakfast, and one group received placebo. The pharmacology department at Deventer Hospital prepared and labeled the prednisone and placebo tablets, which were identical in shape and color, and distributed them to patients in unlabeled boxes. Only the pharmacist could access the allocation table. Both groups of patients received 500 mg of elementary calcium in the evening. The code of randomization was broken after 2 years of treatment, and the prednisone dosage was tapered. Surplus tablets of the study medication were counted at every visit, and adherence was satisfactory (96%). Use of NSAIDs was not regulated. Local glucocorticoid injections were permitted only when absolutely necessary. Physical therapy and additional use of paracetamol were allowed. After 6 months, sulfasalazine (2 g/d) could be prescribed as rescue medication. The decision to add sulfasalazine was made on clinical grounds (activity of rheumatoid arthritis).

Design and Setting

The ethics committees of the University Medical Center Utrecht and the Deventer and Zutphen Hospitals approved the trial. The study was considered ethically acceptable when it was designed (1989 –1991); later, however, it became clear that irreversible joint damage is an early feature of rheumatoid arthritis. With our present knowledge, it would probably be considered unethical to compare the effects of prednisone and placebo in patients who did not receive a disease-modifying antirheumatic drug for at least 6 months. In our study, sulfasalazine could be prescribed as rescue medication only after 6 months to avoid obscuring the effects of prednisone monotherapy.

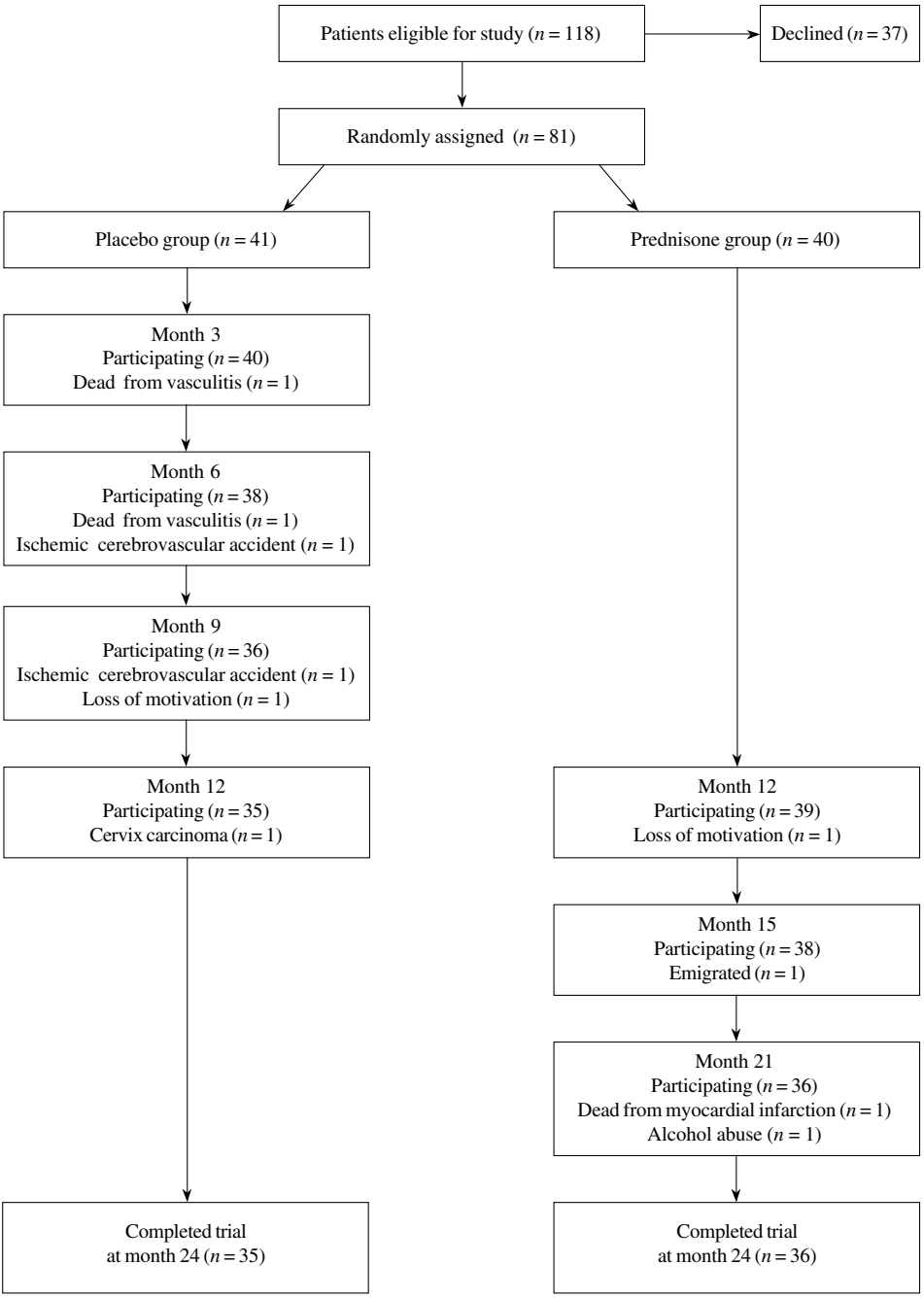


FIGURE 1. Trial profile.

Measurements

All clinical outcome measurements, except those for disability and radiologic outcomes, were performed at baseline and every 3 months. Disability, which was assessed with the Health Assessment Questionnaire, and radiologic outcomes were measured every 6 months. Early-morning stiffness was recorded in minutes (maximum, 720 minutes). Morning pain and general wellbeing were assessed on a horizontal visual analogue scale ranging from 0 to 100 mm, with 0 representing the best score (no problems) and 100 representing the worst score. Swelling and tenderness were assessed with the 28-joint score.[7,8] Grip strength was measured in kPa with a vigorimeter (range, 0 to 200 kPa); the mean of three measurements was calculated for each hand. Disability was assessed with a validated Dutch version of the Health Assessment Questionnaire (Vragenlijst Dagelijks Functioneren),[9] which had a range of 0 to 3 (0 represented the best score [no problems], and 3 represented the worst score). Serum C-reactive protein level was measured in mg/L. To investigate the possible sparing effect of the trial medication, we recorded the use of NSAIDs and analgesics, the frequency of intra-articular corticosteroid injections, and the use of physiotherapy. The patients recorded the use of NSAIDs, analgesics, and physical therapy in standardized patient diaries. To calculate the use of NSAIDs and to compare different NSAIDs, we arbitrarily chose naproxen as a reference. One thousand mg of naproxen was defined as 1 unit and was considered to be approximately equivalent to 600 mg of azapropazone, 100 mg of diclofenac, 200 mg of flurbiprofen, 1600 mg of ibuprofen, 100 mg of indomethacin, 200 mg of ketoprofen, 15 mg of meloxicam, 1000 mg of nabumetone, 20 mg of piroxicam, and 600 mg of tiaprofenic acid. Every 3 months, the first author recorded use of intra-articular corticosteroid injections.

Radiologic outcome measures were erosions, joint space narrowing, and the total score for both (range, 0 to 448). The total score is the sum of the erosions and narrowing scores in 44 joints in the hands and feet, assessed on plain radiography and scored with the van der Heijde modification of the Sharp method.[10,11] Radiologic outcome measures also included the number of patients with erosive disease in each group and the number of radiologically affected joints per patient.

Radiographs were taken at entry and every 6 months. An assistant prepared the radiographs to be read, and all identifying patient data on the radiographs were concealed from the readers. The readers had no knowledge of patient identity when they scored the radiographs. Radiographs were read in random patient order and were scored for each patient in temporal order. Scoring in temporal order clearly has advantages, as a comparative study has shown.[11] However, with this

method, scores can either be stable or increase; a decrease (indicating improvement) is not possible. The first author and an independent radiologist viewed all available radiographs at one center. When the readers' total scores for individual cases differed by 25% or more, agreement was reached through discussion. Joint damage was defined as a score that exceeded 0. To correct for possible differences between the two treatment groups in the number of patients who developed little or no joint damage, we also analyzed data only from patients who developed joint damage. Furthermore, radiologic damage was also analyzed with a cutoff point of 4 modified Sharp units. A score of 0 to 3 was interpreted as no damage, and scores of 4 or greater were interpreted as joint damage. This cutoff point seems to reflect clinically relevant change[12] and was also used in our study to define erosive rheumatoid arthritis.

At the start of the study and every 3 months for 2 years, standardized lists were used to document adverse effects. We noted the occurrence of infections and the use of antibiotics; the latter was checked at the patient's pharmacy. For hypertension, the first author used a single device to measure blood pressure in mm Hg. For steroid diabetes, serum glucose level was measured in mmol/L. Hyperglycemia was defined according to the World Health Organization standard: postprandial, a glucose level of at least 11.0 mmol/L (198 mg/dL), and fasting, at least 6.6 mmol/L (119 mg/dL). Urinary glucose level was measured by using a semiquantitative method (dipstick). A value less than 2.7 mmol/L (49 mg/dL) was considered negative, a value of 2.7 to 5.5 mmol/L (50 to 99 mg/dL) was considered a trace, a value of 5.6 to 16.6 mmol/L (100 to 299 mg/dL) was considered 1+, a value of 16.7 to 54.9 mmol/L (300 to 989 mg/dL) was considered 2+, and a value of 55 mmol/L or greater (≥ 990 mg/dL) was considered 3+. To assess weight gain, body weight in kg was determined with a standardized scale. Gastrointestinal bleeding, ulcers, and peptic symptoms were documented, and the decision to perform gastroscopy was made clinically. Skin disorders were documented, and additional dermatologic expertise was requested when necessary. Hemogram and laboratory variables for kidney and liver function were assessed to monitor for hematologic and biochemical abnormalities. For eye disorders, symptoms and abnormalities were documented; when necessary, additional ophthalmologic expertise was requested. Neuropsychological disorders were recorded.

To assess for osteoporosis, we obtained a radiograph of the spine at baseline and every 6 months for 24 months. We examined vertebrae Th12 through L5. The first author and an independent rheumatologist scored the vertebrae blind, according to the method of Kleerekoper.[13] This method is based on naked-eye inspection of

the vertebrae and comparison of each vertebra with the vertebrae below and above. If an abnormal shape is noticed, the anterior, middle, and posterior heights of that particular vertebra are measured with a ruler. The mean of the heights measured by the two authors was used. The scoring system is as follows: 0 (normal shape and dimensions), 1 (only endplate deformity, middle height, < 85%), 2 (anterior wedge deformity, anterior height, < 85%), and 3 (compression deformity, all 3 heights, < 85%).[13]

Statistical Analysis

All statistical analyses evaluating the effect of treatment were performed according to the intention-to-treat principle. For the 10 patients who withdrew during the study, the outcomes of the last measurements were carried forward, with the exception of the radiologic scores. For radiologic scores, missing data were estimated by using individual progression, as indicated by available scores; if the last measurements had been carried forward, the protective effect of medication on the joints would have been overestimated. Also, "on treatment" analyses were performed to validate the procedures used to estimate the missing data. For radiologic joint damage, which is in itself a cumulative score, and the secondary outcome measures (disability and grip strength), mean differences in changes from baseline between the two groups were tested at 24 months with two-sided t-tests or the Mann–Whitney U-test, where appropriate. For the other outcome measures, changes from baseline over time (24 months) were compared by using the change from baseline in the area under the curve (AUC) as a summary measure. This was done because baseline variables between the two groups favored the prednisone group, although the differences were not statistically significant (**Table 1**).[14] We divided the values for the change in AUC by the number of assessments at follow-up. Since the interval between assessments is identical (3 months), this makes the values for the change in AUC identical to the mean value of the changes occurring in each 3-months interval at follow-up. Therefore, the values for changes in AUC are easily interpretable.

The values for the change in AUC in both groups and the means of radiologic scores for each group at different points in time were tested for statistically significant differences by using unpaired two-sided t-tests or Mann–Whitney U-tests, where appropriate. We calculated the number of patients in each group who had clinically relevant improvement. Clinically relevant improvement was defined as at least 20% improvement in the 28-joint scores for swelling and tenderness and at least 20% improvement in at least two of the four following variables: pain, general wellbeing,

Health Assessment Questionnaire score, and C-reactive protein level. In repeated-measurement analyses of variance, the clinical outcome measurements were used to analyze the relationship between time (disease course) and the effect of the medication (prednisone) on the clinical status of the patient. This allowed us to determine whether patients in the prednisone group showed improvement sooner than patients in the placebo group. To determine whether outcome measurements, patients' characteristics, side effects, and additional therapies statistically significantly differed between groups, we used unpaired, two-sided t-tests or Mann–Whitney U-tests, where appropriate, for the means and Fisher exact tests for proportions. Changes from baseline within groups were tested with paired t-tests or Wilcoxon signed-rank tests, where appropriate. All analyses were performed with the Number Cruncher Statistical System 97 (NCSS Statistical Software, Kaysville, Utah).

RESULTS

Thirty-seven of 118 patients declined to participate in the study for the following reasons: a wish to become pregnant, concern about the side effects of glucocorticoids, the inconvenience of visits to the hospital outpatient department and frequent monitoring, and unwillingness to take the 50% risk for receiving placebo. Patients who declined to participate had a mean age (±SD)of 48 ± 12 years. Twenty-five were women, 28 had IgM rheumatoid factor, and 14 had erosive changes on radiographs of the hands or feet. Compared with study participants, patients who declined participation were younger and more likely to be women. Patient characteristics at the start of the study are shown in **Table 1**. No statistically significant differences were seen between the two groups. All patients were white except for 2 patients in the prednisone group.

Ten patients withdrew from the study, 4 in the prednisone group and 6 in the placebo group (**Figure 1**). Patients in the prednisone group withdrew because of emigration (1 patient at 15 months), loss of motivation (1 patient at 12 months), alcohol abuse (1 patient at 21 months), and death from myocardial infarction (1 patient at 21 months). Patients in the placebo group withdrew because of cervix carcinoma (1 patient lost to follow-up at 12 months), ischemic cerebrovascular accidents that were attributed to arteriosclerosis (1 patient at 6 months and 1 patient at 9 months), loss of motivation (1 patient at 9 months), and rheumatoid arthritis vasculitis (1 patient who died at 3 months and 1 patient who died at 6 months despite aggressive immunosuppressive therapy). Of the 10 patients who withdrew, 1 patient in the prednisone group (alcohol abuse) and 1 in the placebo group (loss

TABLE 1

Baseline Characteristics of the 81 Patients with Early Rheumatoid Arthritis*

Characteristic	Prednisone Group(n = 40)	Placebo Group(n = 41)
Age, y	60 ± 14	64 ± 12
Male/female, n/n	17 / 23	12 / 29
IgM rheumatoid factor, n†	29	31
Erosive disease, n‡	16	15
Early-morning stiffness, min	100 ± 62	117 ± 71
Morning pain, mm§	28 ± 20	34 ± 25
General wellbeing, mm§	31 ± 23	41 ± 23
28-Joint score for swelling	7.3 ± 3.7	8.6 ± 4.3
28-Joint score for tenderness	8.9 ± 5.7	8.6 ± 5.0
Grip strength, kPa	49 ± 24	47 ± 24
Disability score £	0.8 ± 0.6	1.0 ± 0.7
C-reactive protein level, mg/L	11 ± 18	20 ± 28
Radiologic score for hands and feet¶	11 ± 11	15 ± 21
Hypertension, n**	5	11
Chronic obstructive pulmonary disease, n	1	2
History of documented peptic ulcer, n	1 (> 10 years ago)	0
Peptic symptoms treated with medication, n	4	1
Cardiovascular disease, n	1 (coronary bypass)	0

* Values presented with a plus/minus sign are the mean ± SD. No statistically significant differences were seen between groups.
† Rheumatoid factor status was considered positive when the IgM rheumatoid factor level was ≥ 25 IU/mL. This cutoff point yielded a false-positive test result for < 5% of the general population.
‡ A Sharp–van der Heijde erosion score of ≥ 4 was considered erosive, and a score of 0 to 3 was considered nonerosive.
§ Measured with the visual analogue scale. Morning pain and general wellbeing in the previous 48 hours were calculated on a scale from 0 to 100 mm, with 0 representing the best score (no problems) and 100 representing the worst score.
£ Measured with a Dutch version of the Health Assessment Questionnaire.[9] Scores ranged from 0 to 3, with 0 representing the best score (no problems) and 3 representing the worst score.
¶ Erosions and joint space narrowing were assessed by using the van der Heijde modification of the Sharp method.[10,11] Scores ranged from 0 (no damage) to 448 (maximum score for erosions and joint space narrowing in hands and feet).
** These patients were normotensive with medication at the start of the study.

of motivation) received sulfasalazine as rescue medication at 15 and 6 months, respectively. No patients left the study because of adverse effects related to the study medication. After 6 months, 39 of the 71 patients who completed the study (20 in the placebo group and 19 in the prednisone group) received sulfasalazine as additional antirheumatic therapy.

TABLE 2

Effects of Prednisone Treatment in Patients with Early Rheumatoid Arthritis*

Variable	Prednisone Group (n = 40)	Placebo Group (n = 41)	95% CI for the Difference	P Value
Changes from baseline				
12 months				
Radiologic damage	8 ± 13	15 ± 15		0.008
Grip strength, *kPA*	13 ± 21	-1 ± 19	5 to 23	0.002
Functional disability†	0.1 ± 0.6	0.1 ± 0.6		>0.2
24 months				
Radiologic damage	16 ± 23	29 ± 26		0.007
Grip strength, *kPA*	13 ± 19	4 ± 24	0 to 19	0.05
Functional disability†	0.1 ± 0.7	0.0 ± 0.6		>0.2
Change in AUC at 24 months‡				
Early-morning stiffness, *min*	-43 ± 69	-28 ± 78		>0.2
Morning pain, *mm*§	-5 ± 17	1 ± 22	-2 to 15	0.14
General wellbeing, *mm*§	-1 ± 24	0 ± 18		>0.2
28-Joint score for swelling	-2 ± 4	-1 ± 4	-1 to 2	>0.2
28-Joint score for tenderness	-2 ± 4	0 ± 5	1 to 5	0.01
C-reactive protein level, *g/L*	-1 ± 15	0 ± 24		>0.2
Individual patient improvement, *n/n (%)*£				
At 12 months	13/40 (33)	10/41 (24)	-0.1 to 0.3	>0.2
At 24 months	12/40 (30)	9/41 (22)	-0.1 to 0.3	>0.2
Cumulative use of additional therapy				
Patients receiving physiotherapy, *n/n*				
At 6 months	7/40	12/41	-0.3 to 0.1	>0.2
At 24 months	12/40	19/41	-0.4 to 0.0	0.17
Physiotherapy sessions, *n*				
At 6 months	108	308		
At 24 months	701	771		
Patients receiving intra-articular corticosteroid injections, *n/n*¶				
At 6 months	2/40	11/41	-0.4 to -0.1	0.01
At 24 months	8/40	12/41	-0.3 to 0.1	>0.2
Injections, *n*				
At 6 months	2	21		
At 24 months	17	43		
Patients taking paracetamol, *n/n***				
At 6 months	23/40	23/41	-0.2 to 0.2	>0.2
At 24 months	25/40	24/41	-0.2 to 0.3	>0.2
Paracetamol tablets, *n*				
At 6 months	772	2546		
At 24 months	4237	8334		

Clinical Efficacy

For most clinical variables, the changes from base-line favored the prednisone group at 12 and 24 months but did not differ significantly between the two groups. Exceptions were grip strength and the 28-joint score for tenderness; for these variables, a larger, statistically significant improvement was seen in the prednisone group compared with the placebo group (**Table 2**). A statistically significant interaction of time and medication was seen for three clinical variables: pain, 28-joint score for tenderness, and grip strength. Plots of these variables in time showed that this was due to more rapid improvement during the first 6 months in the prednisone group than in the placebo group (data not shown). Individual patient improvement was 33% in the prednisone group and 24% in the placebo group at 12 months and 30% and 22%, respectively, at 24 months (**Table 2**).

Overall use of physiotherapy was significantly lower in the prednisone group than in the placebo group, especially in the first 6 months. At 24 months, the difference in the total number of sessions of physiotherapy was not as pronounced but continued to favor the prednisone group. In the first 6 months, 2 intra-articular corticosteroid injections were administered in the prednisone group and 21 were administered in the placebo group. The total number of intra-articular injections given in the prednisone group at 24 months was 40% lower than that in the placebo group. A total of 772 paracetamol tablets were taken in the first 6 months in the prednisone group compared with 2546 in the placebo group. At 24 months, use of paracetamol in the prednisone group was 49% lower than that in the placebo group. The overall use of NSAIDs over 24 months was also considerably lower in the prednisone group than in the placebo group (**Figure 2**).

* Values presented with a plus/minus sign are the mean ± SD. Unpaired two-sided t-tests were used for normal distribution of the data, and Mann–Whitney U-tests were used for non-normal distribution; in the latter cases, no 95% CIs for the difference are given. AUC = area under the curve.

† Measured with a Dutch version of the Health Assessment Questionnaire. Scores ranged from 0 to 3, with 0 representing the best score (no problems) and 3 representing the worst score.[9]

‡ The values for the change in AUC were divided by the number of assessments at follow-up, making them identical (since the interval between assessments [3 months] is identical) to the mean value of the changes occurring in each 3-month interval at follow-up. This was done to simplify interpretation of the data.

§ Measured with the visual analogue scale. Morning pain and general wellbeing in the previous 48 hours were assessed on a scale of 0 to 100 mm, with 0 representing the best score (no problems) and 100 representing the worst score.

£ Improvement is defined as ≥ 20% improvement in the 28-joint score for swelling and the 28-joint score for tenderness and ≥ 20% improvement in ≥ 2 of the 4 following variables: visual analogue scale score for pain, visual analogue scale score for general wellbeing, disability score, and C-reactive protein level.

¶ A corticosteroid injection was defined as 40 mg of triamcinolone acetonide or equivalent.

** The use of nonsteroidal anti-inflammatory drugs is reported in Figure 2. Two patients in each group used additional analgesics (pentazocine, 50 mg; tramadol, 50 mg; or dextropropoxyphene, 150 mg).

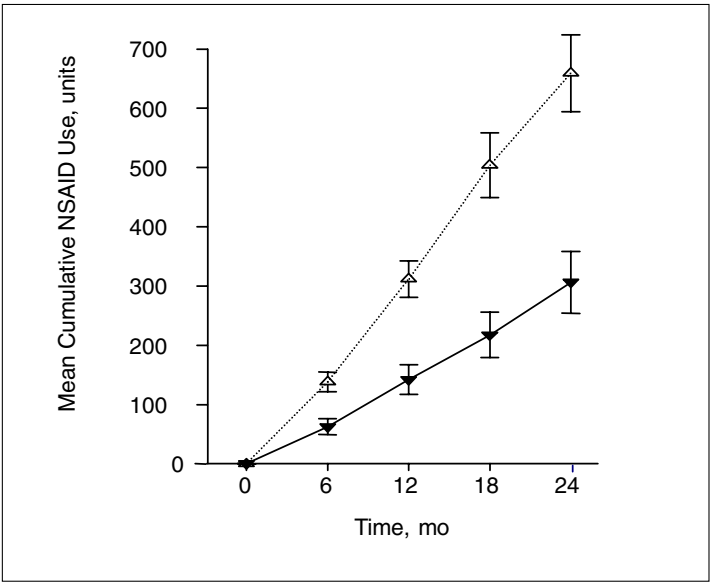


Figure 2. Cumulative mean use of nonsteroidal anti-inflammatory drugs (NSAIDs) in units. One unit = 1000 mg of naproxen or the equivalent dose of another NSAID. At follow-up at all points in time, statistically significant differences were seen between the two groups ($P < 0.001$ [Mann–Whitney U-test]). The solid line indicates the prednisone group; the dotted line indicates the placebo group. Error bars represent the standard error.

Disease-Modifying Properties

Fifty patients (24 in the prednisone group [60%] and 26 in the placebo group [63%]) had nonerosive disease at the start of the study. At 24 months, 30% of patients in the prednisone group and 22% in the prednisone group still had nonerosive disease. At baseline, the mean total score for radiologic outcome measures (the combination of the scores for joint space narrowing and erosions) was slightly higher for the placebo group than for the prednisone group, although the difference was not statistically significant (**Table 1**). From month 12 on, radiologic scores showed significantly less progression in the prednisone group than in the placebo group. Mean changes (±SD) from baseline in modified Sharp scores were 8 ± 13 and 15 ± 15 at 12 months for the prednisone and placebo groups, respectively ($P = 0.008$; effect size, 0.52) and 16 ± 23 and 29 ± 26, respectively, at 24 months ($P = 0.007$; effect size, 0.56) (**Table 2**).

Radiologic scores over time are shown in **Figure 3**. At 12 months, the total mean score (±SD) for radiologic damage was 19 ± 19 for the prednisone group

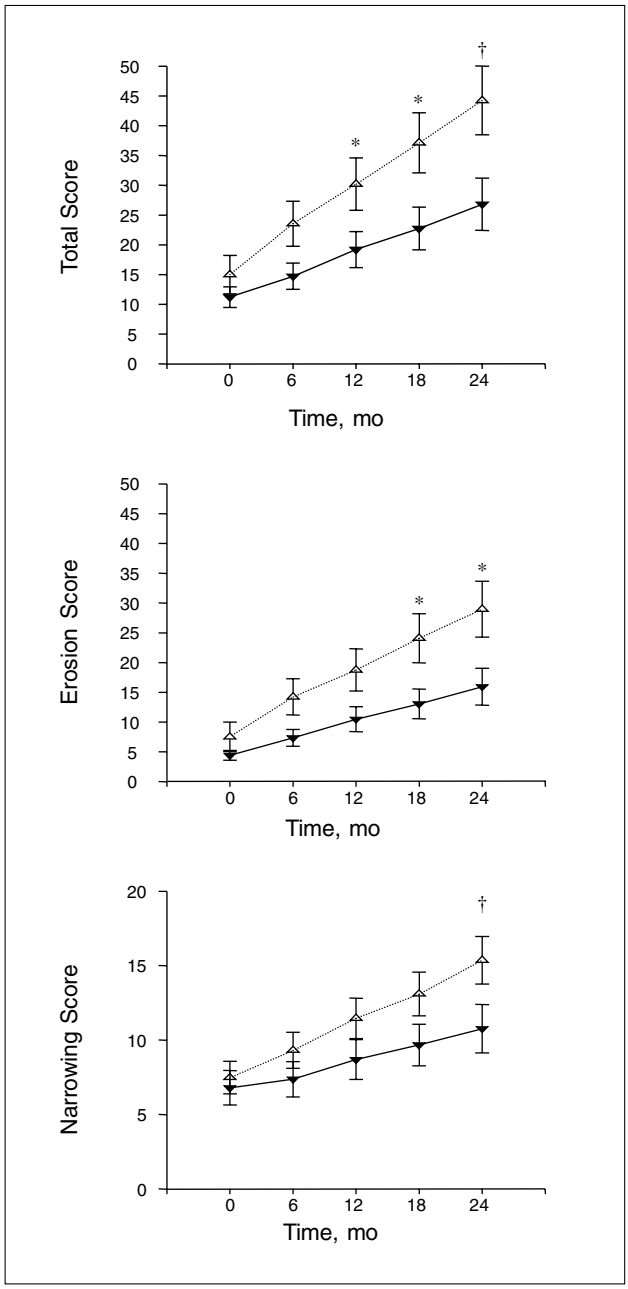


Figure 3. All scores are means and are based on the van der Heijde modication of the Sharp method.[10,11] Solid lines indicate the prednisone group; dotted lines indicate the placebo group. Error bars represent the standarderror. * P = 0.04; † P = 0.02.

TABLE 3

Adverse Effects and Complications

Adverse Effect or Complication	Events in the Prednisone Group (n = 40)	Events in the Placebo Group (n = 41)
Infections treated with antibiotics, *n/n**		
Skin	0	5 (4 patients)
Respiratory tract	13 (11 patients)	13 (9 patients)
Intestinal tract†	1	2
Urinary tract	3 (2 patients)	2
Gastrointestinal		
Stomatitis‡	0	1
Nausea/vomiting	2	2
Peptic symptoms leading to gastroscopy	7	3
Ulcer with bleeding on gastroscopy	1	2
Diarrhea	0	2
Cardiovascular		
Newly developed hypertension	7	6
Angina pectoris	3	3
Myocardial infarction§	1	0
Ischemic cerebrovascular accident £	0	2
Arterial occlusion in legs	0	1
Calf vein thrombosis	0	2
Heart rhythm disorders	1	2
Congestive heart failure	1	1
Ankle edema	1	0
Skin (excluding infections)		
Ulcus cruris	3	2
Exanthema	2	1
Petechiae	1	1
Ophthalmologic		
Glaucoma	1	0
Cataract	1	1
Vitreous humor hemorrhage¶	1	0
New osteoporotic fractures**		
Vertebral	7 (5 patients)	4 (2 patients)
Peripheral (pelvis)	1	0
Miscellaneous		
Impotence††	0	2
Depression	1	2
Concentration disorders	0	1
Cervix carcinoma‡‡	0	1
Medication-dependent diabetes mellitus	2	1
Systemic vasculitis§§	0	2

and 30 ± 28 for the placebo group *(P* = 0.04). At 24 months, the scores were 27 ± 28 and 44 ± 37, respectively *(P* = 0.02) (**Figure 3**, *top*). The mean score for erosions at 12 months was 11 ± 13 in the prednisone group and 19 ± 23 in the placebo group *(P* = 0.08). At 24 months, the scores were 16 ± 20 compared with 29 ± 30, respectively *(P* = 0.04) (**Figure 3**, *middle*). The mean scores for joint space narrowing were 9 ± 9 in the prednisone group and 11 ± 9 in the placebo group at 12 months *(P* = 0.06) and 11 ± 10 and 15 ± 10, respectively, at 24 months *(P* = 0.02) (**Figure 3**, *bottom*). The mean total numbers of affected joints per patient in the prednisone group and the placebo group were 10 ± 7 and 13 ± 8 at 12 months *(P* = 0.05) and 12 ± 9 and 16 ± 9 at 24 months *(P* = 0.047), respectively. Similar differences in all radiologic scores between the two groups were found by "on treatment" analyses *(n* = 71), analyses only of patients de-veloping joint damage, and analyses of radiologic damage with a cutoff point of 4 (0 to 3, no damage; ≥ 4, joint damage) (data not shown).

Adverse Effects

We compared body weight, serum glucose levels, and blood pressure at the start of the study and after 24 months of treatment. In the prednisone group, the mean body weight (±SD) increased significantly from baseline, from 77 ± 19 kg to 80 ± 20 kg *(P* = 0.001). In the placebo group, no statistically significant change was seen. Also in contrast to the placebo group, the mean serum glucose level (±SD) increased significantly in the prednisone group, from 5.1 ± 0.6 mmol/L to 5.9 ± 1.9 mmol/L (92 ± 11 mg/dL to 106 ± 34 mg/ dL) *(P* = 0.01). Hyperglycemia, as defined by the World Health Organization, developed in 2 patients in the prednisone group and 1 in the placebo group. The other variables did not change significantly in either group. At the start of the study, 1 patient in each group had one vertebral

* The number of infections not treated with antibiotics, such as the common cold, was similar in both groups.
† No cultures were taken.
‡ Stomatitis was caused by allergy, probably to a nonsteroidal anti-inflammatory drug used, according to the patient's dermatologist.
§ Cause of death. The patient was 76 years of age.
£ Cause of withdrawal from the study. The patients were 72 and 73 years of age.
¶ Probably not related to the study medication.
** Vertebral fractures Th12 to L5, assessed according to the Kleerekoper method.[13] At the start of the study, one patient in each group had a vertebral fracture.
†† Impotence was not included in the standardized diary but was spontaneously reported by these two patients.
‡‡ Cause of withdrawal from the study.
§§ Cause of death. The patients were 62 and 78 years of age.

fracture (from Th12 to L5). After 24 months, the number of new vertebral fractures was higher in the prednisone group than in the placebo group. Five patients in the prednisone group had new fractures in the spine; of these 5 patients, 3 had a single fracture and 2 had two fractures. The patient in the prednisone group with a fracture at baseline did not develop new fractures. In the placebo group, 2 patients had new vertebral fractures. One was the patient with a fracture at baseline who developed another fracture; the other patient developed three fractures. Except for one osteoporotic fracture of the pelvis in the prednisone group, no osteoporotic fractures outside the spine (forearms, ribs, pelvis, or hips) were seen (**Table 3**).

Other adverse effects are shown in **Table 3**. There were minor infections in both groups. Patients in the prednisone group had no serious skin infections, but erysipelas was seen five times in 4 patients in the placebo group. The numbers of infections in the respiratory, gastrointestinal, and urinary tracts were approximately equal in the two groups. Three patients (1 in the prednisone group and 2 in the placebo group) developed peptic ulcer disease with bleeding, which was confirmed by gastroscopy. The numbers of patients with newly developed hypertension during the study were approximately equal (7 in the prednisone group and 6 in the placebo group). At the start of the study, 11 patients in the placebo group and 5 in the prednisone group were normotensive because of medication for essential hypertension, and they remained stable during the study. In the prednisone group, 1 patient (76 years of age) died after 21 months of a myocardial infarction (confirmed at autopsy). During the study, 3 patients (2 in the prednisone group and 1 in the placebo group) developed diabetes mellitus, which was managed with oral antidiabetic agents and diet; no insulin treatment was needed. Except for infections, the two groups had an equal number of adverse effects affecting the skin, which were well controlled with conservative treatment. Serum aminotransferase levels were elevated in 1 patient in the prednisone group and 1 in the placebo group; values were less than two times the upper limit of normal. Mean serum creatinine concentration did not increase during the study in either group. No other biochemical or hematologic abnormalities were seen during the study. One patient in the prednisone group had glaucoma that was well controlled with conservative treatment, and 1 patient in each group had a cataract. One patient in the prednisone group had a hemorrhage in the vitreous humor in the right eye that caused partial loss of vision, but this complication was probably unrelated to the study medication. No disorders of the central nervous system were observed. For patients with newly developed depressive symptoms (1 in the prednisone group and 2 in the placebo group), no medication was needed.

DISCUSSION

The Medical Research Council and Nuffield Foundation trials in the mid-1950s and mid-1960s suggested a possible disease-modifying role for glucocorticoids. It is difficult to interpret the results of these trials, however, because of the heterogeneity of the patient groups, the long duration of disease at the start of the studies, confounding by indication, and multiple concomitant therapies. In 1995, in a double-blind, placebo-controlled study of 128 patients with early rheumatoid arthritis (average disease duration, 1.3 years), Kirwan demonstrated a significant reduction in progression of radiologic joint damage in the hands when glucocorticoids were added to antirheumatic treatment.[15] Patients received prednisone (7.5 mg/d) or placebo for 2 years in addition to NSAIDs (95% of patients) and disease-modifying antirheumatic drugs (71% of patients).

After 2 years, both the total number of new erosions and the number of patients with erosions were significantly lower in the glucocorticoid group. Clinical variables improved only during the first year of therapy. Kirwan concluded that a fixed daily dose of 7.5 mg of prednisone given as adjuvant therapy for early active rheumatoid arthritis retards radiologic progression of joint destruction. However, only hands were evaluated for the radiologic score. In a 1998 follow-up study by Hickling and coworkers,[16] joint destruction resumed after the prednisone dosage was tapered and therapy was discontinued.

In 1996, Saag and associates[17] reviewed the literature systematically and performed a meta-analysis of the effectiveness of low-dose glucocorticoids in rheumatoid arthritis. Glucocorticoids seemed to be at least as effective as other therapies in improving disease activity. However, data were limited because the treatment episodes were relatively short (7 months on average) and glucocorticoids were given late in the disease course, often in combination with disease-modifying antirheumatic drugs.

In a randomized study of early rheumatoid arthritis, Boers and colleagues[18] compared the effect of sulfasalazine monotherapy with that of combined therapy with prednisone, methotrexate, and sulfasalazine. Prednisone was started at an initial dosage of 60 mg/d, which was tapered in six steps over 6 weeks to 7.5 mg/d, and was withdrawn at week 28. The combined therapeutic regimen slowed radiologic damage significantly more than sulfasalazine alone at weeks 28, 56, and 80. Haagsma and coworkers[13] and Dougados and associates[19], however, found no differences in effect between sulfasalazine and the combination of sulfasalazine and methotrexate in patients with rheumatoid arthritis. Therefore, the difference in effectiveness

between combination therapy and sulfasalazine in the study by Boers and colleagues was probably due to the effect of prednisone. In addition, the combined therapy offered better disease control. In contrast to our present study, the cohort of patients with rheumatoid arthritis in the study by Boers and colleagues was younger and had more active disease. Patients received prednisone at an initial dosage of 60 mg/d, which was tapered; treatment was stopped at 28 weeks. During that 1-year study, the effect of combination therapy on progression of joint destruction persisted after 28 weeks but clinical remission ended in most patients.

Our study is unique because it did not include concomitant therapy with disease-modifying antirheumatic drugs at study entry. We were therefore able to assess the effects of steroids on joint damage independent of disease-modifying antirheumatic drugs. In our study, most patients taking low-dose prednisone needed less additional therapy and showed temporary improvement in most disease variables when compared with the placebo group, although the differences were not statistically significant for all variables. This may be due to more intensive use of additional therapies, including NSAIDs, in the control group (**Table 2** and **Figure 2**). The clinical improvement seen in the studies by Kirwan[15] and by Boers and colleagues[18] lasted longer, for more than 6 months but less than 1 year, at which point the treatment groups no longer differed from the control groups. Compared with prednisone as monotherapy, combination of glucocorticoids with disease-modifying antirheumatic drugs or biological agents in early active rheumatoid arthritis might prolong the clinical benefit. The remarkable retardation of radiologically detected joint destruction in our study was similar to that observed in the studies by Kirwan[15] and by Boers and colleagues.[18] The difference between the two groups in our study even increased gradually until the end of the second year. We do not advocate use of glucocorticoids as monotherapy, however. In our opinion, glucocorticoids, because of their limited disease-modifying effects, should be combined with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis.

In our study, glucocorticoid-induced osteoporosis was a major side effect. We prescribed calcium supplementation for all patients, but if we were performing this study today, we would use more intensive treatment, such as bisphosphonates. This would probably result in fewer signs and symptoms of osteoporosis.

Glucocorticoids suppress a wide variety of nonspecific inflammatory responses (such as cell trafficking and prostaglandin production), as well as specific immune processes, with emphasis on cytokine modulation. At a cellular level, glucocorticoids inhibit the access of leukocytes to inflammatory sites; modulate the functions of leukocytes, endothelial cells, and fibroblasts; inhibit the production and functioning

of a variety of pro-inflammatory cytokines while enhancing the production of anti-inflammatory mediators; and suppress the synthesis of cartilage-degrading metalloproteases by fibroblasts and articular chondrocytes. Taken together, these effects induce the marked clinical amelioration of rheumatoid arthritis[21] and may also explain the protection of bone and cartilage against inflammation-induced degradation, which in turn may explain the drugs' disease-modifying properties.

In conclusion, low-dose prednisone alleviates symptoms of rheumatoid arthritis and has disease-modifying properties. Further investigation of long-term low-dose glucocorticoid therapy in rheumatoid arthritis that examines not only symptoms but especially joint damage and functional outcome is needed.

REFERENCES

1. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum. 1998;41:1552-63. [PMID: 9751087]
2. Bresnihan B, Alvaro-Gracia JM, Cobby M, Doherty M, Domljan Z, Emery P, et al. Treatment of rheumatoid arthritis with recombinant human interleukin- 1 receptor antagonist. Arthritis Rheum. 1998;41:2196-204. [PMID: 9870876]
3. Hench PS, Kendall EC, Slocumb CH, Polley HF. Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions: a study in clinical physiology. Arch Intern Med. 1950;85:546-66.
4. Kirwan JR. Conceptual issues in scoring radiographic progression in rheumatoid arthritis. J Rheumatol. 1999;26:720-5. [PMID: 10090190]
5. Bijlsma JW. Long-term glucocorticoid treatment of rheumatoid arthritis: risk or benefit? Rheumatology in Europe. 1998;27:67-9.
6. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24. [PMID: 3358796]
7. Smolen JS, Breedveld FC, Eberl G, Jones I, Leeming M, Wylie GL, et al. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum. 1995;38:38-43. [PMID: 7818569]
8. Prevoo ML, van Riel PL, van 't Hof MA, van Rijswijk MH, van Leeuwen MA, Kuper HH, et al. Validity and reliability of joint indices. A longitudinal study in patients with recent onset rheumatoid arthritis. Br J Rheumatol. 1993; 32:589-94. [PMID: 8339131]

9. Bijlsma JW, Oude Heuvel CH, Zaalberg A. Development and validation of the Dutch questionnaire capacities of daily life (VDF) for patients with rheumatoid arthritis. Journal of Rehabilitation Science. 1990;3:71-4.
10. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol. 1999;26:743-5. [PMID: 10090194]
11. van der Heijde D, Boonen A, Boers M, Kostense P, van der Linden S. Reading radiographs in chronological order, in pairs or as single films has important implications for the discriminative power of rheumatoid arthritis clinical trials. Rheumatology (Oxford). 1999;38:1213-20. [PMID: 10587548]
12. van der Heijde DM, van Riel PL, van Leeuwen MA, van 't Hof MA, van Rijswijk MH, van de Putte LB. Prognostic factors for radiographic damage and physical disability in early rheumatoid arthritis. A prospective follow-up study of 147 patients. Br J Rheumatol. 1992;31:519-25. [PMID: 1386548]
13. Kleerekoper M, Parfitt AM, Ellis BI. Measurement of vertebral fracture rates in osteoporosis. In: Christiansen C, Arnaud CD, Norden BE, Parfitt AM, Peckn WA, Riggs BL, eds. Copenhagen International Symposium on Osteoporosis. 1984:103-9.
14. Pham B, Cranney A, Boers M, Verhoeven AC, Wells G, Tugwell P. Validity of area-under-the-curve analysis to summarize effect in rheumatoid arthritis clinical trials. J Rheumatol. 1999;26:712-6. [PMID: 10090188]
15. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med. 1995;333:142-6. [PMID: 7791815]
16. Hickling P, Jacoby RK, Kirwan JR. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. Arthritis and Rheumatism Council Low Dose Glucocorticoid Study Group. Br J Rheumatol. 1998;37:930-6. [PMID: 9783756]
17. Saag KG, Criswell LA, Sems KM, Nettleman MD, Kolluri S. Low-dose corticosteroids in rheumatoid arthritis. A meta-analysis of their moderate-term effectiveness. Arthritis Rheum. 1996;39:1818-25. [PMID: 8912503]
18. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet. 1997;350:309-18. [PMID: 9251634]
19. Haagsma CJ, van Riel PL, de Jong AJ, van de Putte LB. Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. Br J Rheumatol. 1997;36:1082-8. [PMID: 9374925]

20. Dougados M, Combe B, Cantagrel A, Goupille P, Olive P, Schattenkirchner M, et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. Ann Rheum Dis. 1999;58:220-5. [PMID: 10364900]
21. Bijlsma JW, van Everdingen AA, Jacobs JW. Corticosteroids in rheumatoid arthritis. How best to use them? Clinical Immunotherapy. 1995;3:271-86.

Low-dose glucocorticoids in early rheumatoid arthritis: discordant effects on bone mineral density and fractures ?

CHAPTER 3

AA van Everdingen
DR Siewertsz van Reesema
JWG Jacobs
JWJ Bijlsma

Submitted

Abstract

To investigate the incidence of osteoporotic fractures and effects on bone of low-dose glucocorticoid (GC) in a group of previously untreated patients with early active RA we performed a double blind, randomised, placebo-controlled clinical trial. The study duration was 2 years, with an open follow-up during the third year. Patients were randomly allocated to receive 10 mg prednisone or placebo.

Non-steroidal anti-inflammatory drugs (NSAIDs) were allowed in both groups. After 6 months sulphasalazine (2 gr daily) could be prescribed as rescue therapy in both groups. Except for 500 mg calcium supplement daily, no specific preventive measures were taken.

At the start of the study and every 6 months, X-rays of the twelfth thoracic and of all lumbar vertebrae were scored using the Kleerekoper method, and every year biochemical parameters of bone metabolism and bone mineral density (BMD) were assessed.

In the prednisone group there was a higher incidence during the study of lumbar vertebral fractures than in the placebo group: 7 vs 4 respectively. This difference did not reach statistical significance however, probably because of the small numbers. One patient of the prednisone group suffered an osteoporotic fracture of the pelvis. In the 2-year study and the subsequent follow-up year, no other peripheral fractures were seen in either group. No significant changes from baseline in BMD of the hips and lumbar spine were seen in either group during the study and the follow-up year: BMD values in both groups did not differ significantly during the whole study. No correlation between changes in serum osteocalcin and BMD was observed.

Low-dose prednisone for patients with early active previously untreated RA seems also to increase the risk of fractures independent of the BMD.

INTRODUCTION

In rheumatoid arthritis (RA) periarticular as well as generalised bone loss is an early feature of the disease with an increased risk of fractures of 1.5 to 2.1.[1-3] Bone formation is normal or reduced and bone resorption is increased in RA patients compared to healthy controls. Bone loss is the result of this uncoupling between bone formation and resorption. The aetiology of generalised bone loss in RA is multifactorial. Inflammation with circulating cytokines and hypogonadism as well as general factors such as decreased physical and weight-bearing activity, age, vitamin D status, hormonal status and physical impairment play a role.[4,5]

Another risk factor for osteoporosis is treatment with glucocorticoids (GC); in general this therapy doubles the risk of fractures.[6] However there is still debate as to whether low-dose GC treatment of an active inflammatory disease also results in the development of osteoporosis and an increased risk of fractures. In contrast to the negative effects on bone, low-dose GC treatment of patients with RA reduces disease activity and joint damage and enhances mobility, effects that are anti-osteoporotic.[7] Therefore, the positive effects of low-dose GC treatment of patients with RA on disease activity and joint damage may counterbalance the negative effects on bone.[3,6,7] In various studies the incidence of clinical manifestations of vertebral fractures was significantly higher in patients with RA treated with GC compared to RA patients without GC.[8,9] However, interpretation of the results of other studies is difficult because of confounding factors such as the administration of prednisone only to patients with more active disease (allocation bias).

The aim of our study, in which prednisone therapy was randomly allocated (thus excluding allocation bias for prednisone) was to investigate the effects on bone and the risk of fractures of low-dose prednisone in patients with early active previously untreated RA.

PATIENTS AND METHODS

Patients

From October 1992 through October 1995 eighty-one out of 118 eligible consecutive outpatients of the Departments of Rheumatology of the Deventer and Zutphen Hospitals, who were at least 18 years of age, had early previously untreated RA (disease duration less than one year), and satisfied the 1986 ARA-classification, were enrolled in the study.[10] Inclusion criteria were: active disease defined as (at least 2 out of 3): 28 joint score for tenderness and 28 joint score for swelling of 3

or more, Westergren erythrocyte sedimentation rate (ESR) 28 mm after one hour or higher and early morning stiffness lasting 30 minutes or longer.[11-12] Exclusion criteria were contraindications for the use of prednisone and/or NSAID's, serious concomitant diseases, active gastrointestinal problems, severe hypertension, haemorrhagic diathesis, treatment with cytotoxic or immunosuppressive drugs, alcohol or drug abuse and severe psychiatric or mental problems.

Informed consent was obtained from all subjects prior to participation. Of the 118 eligible patients, thirty-seven refused to participate.

Intervention

The 81 participating patients were randomly allocated in blocs of 10 subjects by the Pharmacy of the Deventer Hospital to one of two groups for treatment for two years: 1) two tablets of 5 mg prednisone once daily at breakfast (=10 mg), 2) placebo tablets in the same way. The Pharmacology Department prepared and labelled the prednisone and placebo tablets, which were identical in shape, taste and colour. Both groups of patients received 500 mg elementary calcium in the evening to retard GC-induced osteoporosis as was the normal procedure at that time (study designed in 1989-91). According to current knowledge patients would now be treated with bisphosphonates and/or vitamin D and 1000 mg elementary calcium.

The code of randomisation was broken after 2 years of treatment. Dosage was then tapered off for patients receiving prednisone. At every visit the surplus tablets of the study medication were counted; compliance was satisfactory (96%). Use of NSAID's was free. Local CS injections were permitted only if unavoidable. Physical therapy and additional use of paracetamol were allowed and recorded every 3 months. After 6 months sulphasalazine (2 gr. daily) could be prescribed as rescue medication. The decision to add sulphazalazine was based on clinical grounds only (activity of RA).

Design, setting

This prospective, double-blind, randomised, placebo-controlled trial was approved by the Ethics Committees of the University Medical Center Utrecht and the Deventer and Zutphen Hospitals. At the time the study was designed (1989-91), the study design was considered ethically acceptable; later it became clear that irreversible joint damage in RA is an early feature of the disease. With our present knowledge comparison of the effects of prednisone and placebo in patients who did not

TABLE 1

Baseline characteristics of the 81 patients with early RA (number of patients (n) or means and standard deviations). There were no statistically significant differences between the two groups.

Characteristic	Prednisone Group(n = 40)	Placebo Group(n = 41)
Age in years	60 (14)	64 (12)
Male/female (n)	17 / 23	12 / 29
IgM rheumatoid factor positive ‡ (n patients)	29	31
Patients with erosive disease (n)	16	15
28 Joint score for swelling	7 (4)	9 (4)
28 Joint score for tenderness	9 (6)	9 (5)
Vas pain in mm¶	11 (18)	20 (28)
HAQ*	0.8 (0.6)	1.0 (0.7)
CRP in mg/L	28 (20)	34 (25)
Serum creatinine in umol/l#	81 (15)	80 (12)
Serum 25-OH vitamin D@	72 (35)	61 (21)

‡ RF status was considered positive when the IgM-RF was 25 IU/ml or more, a cut-off point resulting in a false-positive test for less than 5% of the general population.

¶ VAS (visual analogue scale) for morning pain and general wellbeing referred to the previous 48 hours on a scale ranging from 0 -100 mm, 0 representing the best (no problems) and 100 the worst score.

* A Dutch version of the HAQ (VDF, Vragenlijst Dagelijks Functioneren), its score ranging from 0-3, 0 representing the best (no problems) and 3 the worst score.[26]

Serum creatinine: normal ≤ 110 male; ≤ 90 female.

@ Normal range: 25-150 nmol/L; only one patient (in the prednisone group) had a subnormal value (23 nmol/L).

receive a DMARD for at least six months would probably be considered unethical. In our study sulphasalazine as rescue medication could be prescribed only after 6 months in order not to obscure the effects of prednisone monotherapy.

Measurements

At the start of the study and every 3 months for three years, variables on disease activity and adverse effects were assessed: the results are reported elsewhere.[7] In this report, baseline values of joint scores, visual analogue scale (VAS) pain (0-100 mm), the HAQ score and serum C-reactive protein are shown in **Table 1**.

At the start of the study and every 6 months radiographs of the lower thoracic and lumbar spine were made and assessed according to the method of Kleerekoper.[13]

The vertebrae (Th 12 through L 5) were scored by naked eye inspection and compared to the vertebrae below and above by two observers (AAvE, DH). The radiographs were prepared for reading by a houseman; data of the patients on the radiographs were blinded from the observers. The observers had no knowledge of the identity of the patients on the radiographs at the time of scoring. Radiographs were read in random patient order and scored for each patient in temporal order: 0 (normal shape and dimensions), 1 (only endplate deformity, middle height < 85%), 2 (anterior wedge deformity, anterior height < 85%) and 3 (compression deformity, all heights < 85%). The maximum score was 18.

At the start of the study and once every year bone mineral density (BMD) of the lumbar spine (L2-4) and collum femoris of both hips was measured by dual-energy X-ray absorptiometry (BMD in g/cm^2) (Hologic QDR-4500A) with a cut-off point for changes from baseline >0.27 g/cm^2. BMD values were expressed as T-scores and changes from baseline. Osteocalcin in serum (mg/L; measured by OStK-Pr radioimmunoassay kit purchased from CIS BIO International, GIP-SUR-Yvette, Cedex France) and excretion of hydroxyproline in 24-hour samples of urine (um/24h/m^2) on a hydroxyproline-poor diet, considered at the time of the study the most reliable markers of bone metabolism, were measured in addition to excretion of calcium and creatinine in 24h urine in mmol/24h.

At the start of the study and every 3 months serum creatinine in umol/L was assessed and at the start of the study also serum 25-OH vitamin D.

Statistical analysis

All statistical analyses to evaluate possible effects of treatment on bone were performed with patients 'on treatment'; 'intention to treat' analysis with estimation of missing data by carrying the last measurement forward would have yielded a too positive result. For the 10 patients in the 2-year study and the 6 patients in the follow-up year who dropped out, the outcomes of clinical variables were estimated conservatively according to the method of last measurements carried forward. Outcome measurements were tested for statistically significant differences between the two groups using unpaired, two-sided T-tests or Mann-Whitney U tests, where appropriate, for the means and Fishers'exact test for proportions.

Correlations were calculated between osteocalcin and BMD and between CRP and BMD using Pearson's correlation coefficients.

All analyses were performed with the statistical package "Number Cruncher Statistical System" version 97 (Jerry Hintze, Kaysville, Utah).

TABLE 2

Bone mineral densities (T-scores) and fractures across time for patients with RA (prednisone vs. placebo)
Time in months, means (standard error of the mean, SEM), number of patients

Time in months	0	12	24	36
T-score Lumbar spine				
-prednisone (n = 32)	-0.8 (0.3)	-1.0 (0.3)	-1.1 (0.3)	-1.1 (0.3)
-placebo (n = 33)	-0.7 (0.3)	-0.6 (0.3)	-0.6 (0.3)	-0.6 (0.3)
T-score Femoral neck				
-prednisone (n = 32)	-1.8 (0.2)	-1.8 (0.2)	-1.9 (0.2)	-1.8 (0.2)
-placebo (n = 33)	-1.9 (0.2)	-1.9 (0.2)	-1.9 (0.2)	-1.9 (0.2)
Cumulative number of Fractures				
-prednisone	1	5	8	10
-placebo	1	2	5	5
Cumulative number of patients with fractures (total number of patients)				
-prednisone	1 (40)	4 (40)	5 (36)	5 (31)
-placebo	1 (41)	2 (36)	2 (35)	2 (33)

RESULTS

Patients' characteristics at the start of the study are shown in **Table 1**: there were no statistically significant differences between groups. All patients were Caucasian except for two in the prednisone group: one Asian and one Mediterranean. Of the 118 patients 37 declined to participate in the study. They had the following characteristics: mean age 48 (SD 12) years; 25 were female; 28 patients had IgM-rheumatoid factor and 14 exhibited erosive changes on radiographs of the hands and/or feet. So, the group of non-participants consisted of relatively more female and younger patients compared to the study group.

Ten patients dropped out of the study: 4 in the prednisone group and 6 in the placebo group, details are described elsewhere.[7] For 65 of the 71 patients all BMD measurements were available. No significant changes from baseline in BMD of the hips and lumbar spine were seen in either group nor significant differences between both groups, see **Table 2**.

At the start of the study there was one patient in each group with one vertebral fracture (Th12-L5). After 24 months, 5 patients in the prednisone group had new fractures in the lumbar spine: 3 patients had a single fracture and 2 had 2 fractures.

The one patient who had a fracture at the start did not develop new fractures. In the placebo group 1 patient had 3 new vertebral fractures and the one patient who had had a fracture at the start of the study had developed a new one. Except for one osteoporotic fracture of the pelvis, no other fractures (forearms, ribs or hip) were seen (**Table 2**). During the follow-up year no new vertebral fractures occurred in the placebo group. In the prednisone group 2 patients who already had vertebral fractures developed a new vertebral fracture.

The first patient entered the 2-year study in 1993; the last patient finished the study in 1998. In 1999 we were able to take radiographs of the thoracic and lumbar spine of 59 out of the 65 patients. There were no new fractures in the placebo group. In the prednisone group there was one thoracic vertebral fracture in a patient who was known to have a lumbar vertebral fracture: 2 patients who had had lumbar vertebral fractures had both developed one new lumbar fracture.

At the start of the study, only one patient (in the prednisone group) had a subnormal 25-OH vitamin D level: 23 (normal: 25-150 nmol/L).

There was a significantly lower serum osteocalcin level at 12 and 24 months in the prednisone group compared to the placebo group (p-value 0.05 and 0.007, respectively). There was also a significantly higher calcium excretion in samples of 24h urine at 24 months in the prednisone group (p-value 0.0008). No statistically significant differences were found for the excretion of hydroxyproline in samples of 24h urine.

No statistically significant correlations were found between serum osteocalcin and BMD and between serum CRP and BMD (data not shown).

DISCUSSION

In our 2-year placebo-controlled (and 1-year follow-up) study, which showed joint protective properties of low-dose prednisone for patients with early previously untreated active RA, we found more vertebral fractures in the prednisone group compared to the placebo group but this (clinically relevant) difference did not reach statistical significance, probably because of the small numbers. No clinically relevant nor statistically significant differences in BMD measurements were found between the group of patients treated with prednisone and the group on placebo. There was a higher disease activity in the placebo group compared to the prednisone group but no clear differences in clinical variables, probably because the use of NSAID's was more than doubled in the placebo group compared to the placebo group to the prednisone group (details reported elsewhere).[7] In inflammatory

diseases such as RA, there is a positive correlation between disease activity, bone turnover and rate of fractures, most of which are vertebral deformities.[6] Probably in our study the negative effect of disease activity on bone that was higher in the placebo group counterbalanced the negative effect of prednisone in the prednisone group: hence no statistically difference between the two groups regarding BMD.

In recent literature the relationship between low-dose GC treatment, the development of low BMD and the risk of fractures is a subject of controversy. Most of these retrospective studies were performed with patients with longstanding RA and the results are controversial.[8,14] We will go into these studies in short.
In several studies on low-dose long-term GC treatment of postmenopausal RA patients, a higher incidence of fractures -especially of the vertebrae and femoral neck- compared to RA patients who did not receive GC and had a lower BMD was reported.[9,15]

In a cohort of patients with a variety of diseases no difference was found in the relationship between changes in BMD and vertebral fractures between patients receiving GC and who were not on this therapy.[16] In contrast, in other studies higher fracture rates than could be expected from the observed changes in BMD were reported,[17,18] as in our study. However, there is a difference between the study population for those studies and our patients, all of whom had previously untreated, active early RA. The fact that our study, which was free of allocation bias, was indicative of a discrepancy between bone strength and BMD in patients on prednisone, seems to confirm the hypothesis that GC treatment may lead to fractures also via effects on bone other than a decrease in BMD, i.e. changes in bone strength and structure.[19] For patients with a variety of diseases who are on long-standing GC treatment, the risk of fractures can be explained for only 40% by the value of BMD, the other 60% by other factors such as the risk of falling (5).
At the time of our study it was standard procedure only to provide a supplement of 500 mg elementary calcium daily for patients with RA treated with GC to prevent osteoporosis. After 1996 a number of well-conducted studies was published showing the efficacy of bisphosphonates in combination with calcium and vitamin D in preventing bone loss and even increasing BMD in patients treated with GC.[20-23] Nowadays it is considered unethical to perform studies with GC without adequate prevention of osteoporosis.

Statistically significant differences were found between the two groups in serum osteocalcin levels and excretion of calcium in 24h samples of urine: lower serum osteocalcin and higher calcium excretion characterised the prednisone group. No

correlations were found in either group between bone markers, disease activity and the BMD. Our finding of a statistically significant decrease in serum osteocalcin and the excretion of calcium in 24h urine for the prednisone group compared to the placebo group contrasts with data in the literature. In a study of postmenopausal women with longstanding RA no significant differences in biochemical markers of bone turnover were observed between RA patients treated with low-dose GC and those receiving placebo.[15] Another study did not find significant differences in excretion of calcium in 24h urine.[24] In a similar study there were no differences in serum osteocalcin between the prednisone and placebo groups.[25] Differences with respect to our study of early RA patients could possibly be explained by a different disease duration: the majority of other studies were performed with patients with longstanding RA.

At this time only one study on the effects of short-term low-dose GC on bone metabolism in patients with active RA has been published.[8]

The hypothesis that the positive effects of GC on disease activity might counterbalance the negative effects on bone might explain the lack of correlation between disease activity (CRP) and bone marker (osteocalcin in serum).

In conclusion, in our study without allocation bias for prednisone, a discrepancy seems to be present between the lack of change in BMD and the increased albeit not statistically significant incidence of fractures in patients with early active RA treated with low-dose prednisone. Apparently mechanisms other than a decreased BMD are also responsible for diminished bone strength and an increased risk of fractures.

REFERENCES

1. Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy and hip fracture. Ann Rheum Dis 1995;54:49-52.
2. Hooyman JR, Melton LJ, Nelson AM, O'Fallon WM, Riggs BL. Fractures after rheumatoid arthritis. Arthritis Rheum 1984;27:1353-61.
3. Jacobs JWG, de Nijs RNJ, Lems WF, Bijlsma JWJ. Bone metabolism in rheumatoid arthritis. Clin Exp Rheumatol 2000;18(Suppl. 21):S5-11.
4. Kroot EEJA, Laan RFJM. Bone mass in rheumatoid arthritis. Clin Exp Rheumatol 2000;18(Suppl. 21):S12-15.
5. Bijlsma JWJ, Jacobs JWG. Hormonal preservation of bone in rheumatoid arthritis. Rheum Dis Clin North Am 2000;26:897-910.

6. Bijlsma JWJ. Prevention of glucocorticoid-induced osteoporosis. Ann Rheum Dis 1997;56:507-9.
7. Everdingen AA van, Jacobs JWG, Siewertsz van Reesema DR, Bijlsma JWJ. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties and side effects. A double-blind placebo-controlled clinical trial. Ann Int Med (accepted for publication 2001).
8. Laan RFJM, Jansen TLTh, van Riel PLCM. Glucocorticosteroids in the management of rheumatoid arthritis. Rheumatol 1999;38:6-12.
9. Lems WF, Jahangier ZN, Jacobs JWG, Bijlsma JWJ. Vertebral fractures in patients with rheumatoid arthritis treated with corticosteroids. Clin Exp Rheumatol 1995;13:293-7.
10. Arnett PC, Edworthy SM, Bloch CH, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
11. Smolen JS, Breedveld PC, Eberl G, et al. Validity and reliability of the twenty-eight joint-count for the assessment of rheumatoid arthritis activity. Arthritis Rheum 1995;38:38-44.
12. Prevoo ML, van Riel PLCM, van 't Hof MA. Validity and reliability of joint indices. A longitudinal study in patients with recent onset rheumatoid arthritis. J Rheumatol 1993;32:580-94
13. Kleerekoper M, Parfitt AM, Ellis BI. Measurement of vertebral fracture rates in osteoporosis. In: Christiansen C, et al., eds. Copenhagen International Symposium on Osteoporosis 1984:103-9.
14. Verhoeven AC, Boers M. Limited bone loss due to corticosteroids: a systemic review of prospective studies in rheumatoid arthritis and other diseases. J Rheumatol 1997;24:1495-503.
15. Verstraeten A, Dequeker J. Vertebral and peripheral bone mineral content and fracture incidence in postmenopausal patients with rheumatoid arthritis: effect of low-dose corticosteroids. Ann Rheum Dis 1986;45:852-7.
16. Selby PL, Halsey JP, Adams KRH, Klimiuk P, Knight SM, Pal B, Stewart IM, Swinson DR. Corticosteroids do not alter the threshold for vertebral fracture. J Bone Miner Res 2000;15:952-6.
17. Peel NF, Moore DJ, Barrington NA, Bax DE, Eastell R. Risk of vertebral fracture and relationship to bone mineral density in steroid treated rheumatoid arthritis. Ann Rheum Dis 1995;54:801-6.

18. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1997;312:1254-9.
19. Buckley LM. Clinical and diagnostic features of glucocorticoid-induced osteoporosis. Clin Exp Rheumatol 2000;18:41-3.
20. Homik JE, Cranney A, Shea B, et al. A meta-analysis on the use of bisphosphonates in corticosteroid induced osteoporosis. J Rheumatol 1999;26:1148-57.
21. Saag KG, Emkey R, Schnitzer TJ, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. N Engl J Med 1998;339:292-9.
22. Cohen S, Levy RM, Keller M, et al. Risedronate therapy prevents corticosteroid-induced bone loss. Arthritis Rheum 1999;42:2309-18.
23. Black DM, Thompson DE, Bauer DC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the fracture intervention trial. J Clin Endocrinol Metab 2000;85:4118-24.
24. Leboff MS, Wade O, Mackowiak S, El-Haj Ful G, Zangari M, Liang MH. Low-dose prednisone does not affect calcium homeostasis or bone density in postmenopausal women with rheumatoid arthritis. Br J Rheumatol 1991;18:339-441.
25. Hall GM, Spector TD, Delmas PD. Markers of bone metabolism in postmenopausal women with rheumatoid arthritis. Effects of corticosteroids and hormone replacement therapy. Arthritis Rheum 1995;38:902-6.
26. Bijlsma JWJ, Oude Heuvel CHB, Zaalberg A. Development and validation of the Dutch questionnaire capacities of daily life (VDF) for patients with rheumatoid arthritis. J Rehabil Sci 1990;3:71-4.

The clinical effect of glucocorticoids on wellbeing in patients with RA may be masked by decreased use of additional therapies

CHAPTER 4

AA van Everdingen
DR Siewertsz van Reesema
JWG Jacobs
JWJ Bijlsma

Submitted

Abstract

Objective

In our former analysis in patients with early active rheumatoid arthritis (RA), treated with 10 mg prednisone or placebo discrepancies between both groups were found. In contrast to a significant retardation of joint damage in the prednisone group compared to the placebo group, there were no differences in clinical variables between the 2 groups, attributable to more use of additional therapy in the placebo group than in the placebo group.
Aim of the study: to investigate whether this discrepancy, regarding different dimensions of RA, would extend to variables of wellbeing.

Methods

A double blind, randomized, placebo-controlled clinical trial, duration 2 years (10 mg prednisone or placebo), including an open follow-up third year of 81 patients with early (≤ 1 year) active previously untreated RA. Forty-one patients were allocated to 10 mg prednisone orally daily and 40 to placebo. Analgesics, NSAIDs, restricted use of local steroid injections and use of physiotherapy were allowed in both groups. After 6 months sulphasalazine (2 gr daily) could be prescribed as "rescue" therapy in both groups. At start and every 6 months thereafter 2 health status questionnaires VDF (Dutch version of the HAQ) and IRGL (Dutch version of the AIMS) were administered and every 3 months a visual analogue scale (VAS) for morning pain. Furthermore, disease activity and radiological scores were assessed.

Results

Scores of the VDF showed no statistically significant differences between the prednisone group and the placebo group. No statistical differences were found in almost all parameters of the IRGL between groups. At 3 months the VAS morning pain and the VAS general wellbeing showed improvement in the prednisone group comparable with the transient improvement in some other disease activity variables. In the prednisone group the cumulative use of NSAIDs, analgesics, local steroid injections and sessions of physiotherapy was about 50% of that of the placebo group.

Conclusion

Although significant retardation of joint damage in the prednisone group indicates better disease control, no differences between both groups were found for variables of wellbeing. This discrepancy can probably be attributed to increased use of additional therapy in the placebo group. So, the use of additional therapies should thus be taken into account in analyzing and interpreting results of clinical drug trials.

INTRODUCTION

In daily clinical practice with patients with rheumatoid arthritis (RA), most physicians assume a direct association between disease activity, general wellbeing and joint damage late in the course of the disease. Therapeutic approaches of patients with RA are based on these assumptions. Frequently, in the treatment of these patients, in addition to disease modifying antirheumatic drugs (DMARDs), glucocorticosteroids (GC) are used for instantaneous relieve of symptoms and for improvement of general wellbeing. Recently, several studies on RA suggest also disease-modifying properties of long-term low-dose GC.[1-5] These studies describe effects on disease activity and joint damage whereas few studies describe the effects on wellbeing [6]. In most of these studies the use of additional therapies such as analgesics, NSAIDs, local injections and physiotherapy are not taken into account. In healthy adult volunteers and non-RA patients the effects of GC on cognitive functioning and psychological side effects have extensively been described and reviewed.[7-8] In our analysis of patients with early active previously untreated RA, we saw no enduring differences in variables of disease activity and physical functioning between the prednisone 10 mg group and the placebo group.[1] In the prednisone group however, better disease control was achieved, as significant retardation of joint damage occurred, compared the placebo group. This discrepancy between radiological and clinical effects could be attributed to the greater amount of analgesics and NSAIDs used in the latter group. It thus makes a difference whether suppression of signs and symptoms is achieved with low dose prednisone or extra analgesics and NSAIDs. This difference might extend to variables of wellbeing. From daily practice, low-dose prednisone could be hypothesized to have more effects on wellbeing than extra analgesics and NSAIDs.

There are more data suggesting that disease activity and wellbeing are not always well balanced or strictly coupled in the course of RA. Androgens as adjuvant treatment led to improvement in general wellbeing of postmenopausal women with active RA but not in disease activity.[9] In a study comparing the use of alternative or complementary therapy (CM) with conventional therapy of patients with RA, a higher impact of RA in the absence of worse disease was perceived by users of CM in several domains of life, especially psychological functioning.[10]

The aim of the present study is to investigate whether the discrepancy found in our analysis between disease activity variables and joint damage also extends to variables of wellbeing and to investigate the role of additional therapies in interpreting results of clinical drug trials.

PATIENTS AND METHODS

Patients

From October 1992 through October 1995, eighty-one out of 118 eligible consecutive outpatients, who were at least18 years of age, with early previously untreated RA (disease duration less than one year), according the 1986 ARA-classification, were enclosed in the study.[1] The patients were recruited from the Departments of Rheumatology of the Deventer and Zutphen Hospitals, the Netherlands, and randomly allocated in blocs of 10 subjects to one of two groups of treatment for two years: 1) two tablets of 5 mg prednisone once daily at breakfast (=10 mg), 2) placebo in the same way. Use of NSAIDs, physical therapy and paracetamol was free of choice. Restricted use of local GC injections was allowed. After 6 months sulphasalazine (2 gr. daily) could be prescribed as additive "rescue" medication. The decision to add sulphasalazine was based on clinical grounds (activity of RA).

Variables

At start and every 6 months thereafter, two validated health status questionnaires were administered:

1) VDF: functional disability assessed with a validated Dutch version of the Health Assessment Questionnaire. The VDF contains of 20 items, which are grouped into 8 scales representing dressing, arising, eating, walking, hygiene, reach, grip and outside activity. Patients are asked about the ability to perform activities without help, with responses 'able to do without difficulty '(score 0), 'able to do with some difficulty '(score 1), 'able to do with much difficulty' (score 2) and 'unable to do' (score 3). Furthermore, patients are asked whether or not they use a cane, a wheelchair, an adapted bed or chair, or devices for dressing, hygiene, or eating and whether or not they are assisted in performing any of the activities of the 8 scales. The total VDF score may vary from 0-3, 0 representing the best (no problems) and 3 the worst score.[11]
2) IRGL: Impact of Rheumatic diseases on General health and Lifestyle. The IRGL is a health status questionnaire, developed from the Arthritis Impact Measurement Scales 1 (AIMS 1) assessing physical, psychological and social functioning as well as the impact of the disease on daily life.[12] The scales of the IRGL differ in their individual ranges and are expressed in the original direction: for example, high values on the scale pain and low values on the scale mobility and self care indicate a poor health status. The IRGL has been validated in the Netherlands.[13]

The IRGL assesses the various domains of health as follows:

- Physical wellbeing: 21 items: 7 for the scale mobility, 8 for the scale self care and 6 for the scale pain
- Psychological wellbeing: 22 items: 6 for the scale depressive mood, 6 for the scale cheerful mood and 10 for the scale anxiety
- Social wellbeing: 13 items: 2 for quantitative aspects of the scale of social support and 11 for qualitative aspects forming 3 scales: potential exchange of emotional support, actual exchange of emotional support and mutual visits
- Arthritis Impact: 12 items of the impact of RA on daily life: work, housekeeping, hobbies, holidays, leisure, sexuality, eating and sleeping habits, relationships with the partner, family and friends and family life

We also assessed every 3 months a visual analogue scale (VAS) for early morning pain and one for general wellbeing regarding the past week, both scales ranging from 0 to 100 mm, 0 representing the best and 100 the worst score.
From start and every 3 months thereafter the number of NSAIDs, analgesics, physical therapy and local intraarticular injections was assessed.

As parameters for disease activity were assessed C- reactive protein (CRP), early morning stiffness recorded in minutes, the 28 joint score for tenderness and the 28 joint score for swelling and grip strength. At start and every 6 months thereafter, radiographs of hand and feet were performed and scored according to the Sharp/van der Heijde method.[1, 14- 16]

Statistical analysis

All statistical analyses to evaluate the effect of treatment were performed according to the 'intention to treat 'principle. For the 10 patients who dropped out during the study, outcomes of the last measurements were carried forward, with the exception of the radiological scores. For radiological scores, missing data were estimated using individual progression as indicated by available scores; last measurements carried forward would have been too positive as estimation, suggesting no further deterioration. For the VDF, IRGL, the VAS morning pain, the VAS general wellbeing, CRP, early morning stiffness, the 28 joint score for swelling and the 28 joint score for pain, mean differences in changes from baseline between the two groups were tested at 24 months with two-sided T-tests or the Mann-Whitney U-test, where appropriate (see **Table 1**).

Baseline variables and patients' characteristics were tested for statistically significant differences between the two groups using unpaired, two-sided T-tests or Mann-Whitney U tests, where appropriate, for means and with Fishers' exact

TABLE 1

Baseline characteristics of the 81 patients with early RA γ (numbers, means and standard deviations)

	Prednisone n = 40	Placebo n = 41
Age in years	60 (14)	64 (12)
Male/female (n)	17 / 23	12 / 29
IgM rheumatoid factor positive ‡ (n patients)	29	31
Patients with erosive disease (n) #	16	15
Variables of wellbeing		
- Disability score (VDF)*	0.8 (0.6)	1.0 (0.7)
- IRGL mobility°	21.6 (6)	19.2 (6)
- IRGL self care°	25.6 (5)	25.6 (5)
- IRGL pain°	14.9 (4)	16.7 (4)
- VAS morning pain³	28 (20)	34 (25)
- VAS general wellbeing ¶	31 (23)	41 (23)

γ no statistically significant differences between the two groups

‡ RF status was considered positive when the IgM-RF was 25 IU/ml or more, a cut-off point resulting in a false-positive test for less than 5% of the general population.

* VDF (Vragenlijst Dagelijks Functioneren) is a Dutch version of the HAQ questionnaire, its score ranging from 0-3, 0 representing the best (no problems) and 3 the worst score [11].

Sharp-van der Heijde erosion score of ≥ 4 was considered to be erosive and 0-3 non-erosive [6].

° IRGL Impact of Rheumatic diseases on General health and Lifestyle; mobility, range 7-28, 7 representing the worst score and 28 the best score; self care, range 8-32, 7 representing the worst score and 28 the best score; pain, range 6-25, 6 representing the worst score and 25 the best score [12].

³ Visual analogue scale (VAS) of morning pain 0-100 mm., 0 the best score, 100 the worst score

¶ Visual analogue scale (VAS) of general wellbeing 0-100mm, 0 the best score, 100 the worst score

tests for proportions). Individual patient improvement was assessed according to the modified 20% ACR improvement criteria: details are described in our earlier report.[1]

All analyses were performed with the statistical package "Number Cruncher Statistical System" version 97 (Jerry Hintze, Kaysville, Utah).

RESULTS

Patient characteristics, VDF, VAS early morning pain, VAS general wellbeing and 3 domains of the IRGL at the start of the study are shown in **Table 1**: there were no statistically significant differences between the two groups. All patients were Caucasian except for two in the prednisone group.

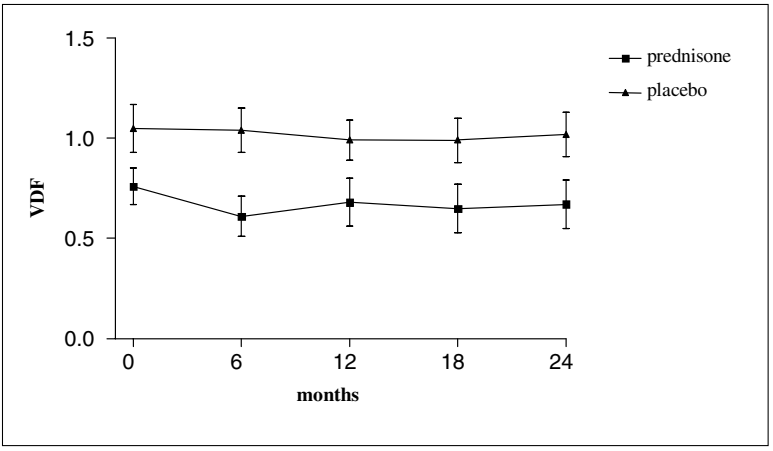


Figure 1. The VDF (a Dutch version of the HAQ) of patients with early RA treated with prednisone compared to placebo (means, SEM). There were no statistically significant differences between both groups VDF (Vragenlijst Dagelijks Functioneren) is a Dutch version of the HAQ questionnaire, its score ranging from 0-3, 0 representing the best (no problems) and 3 the worst score.[11]

Ten patients discontinued the study: 4 in the prednisone group and 6 in the placebo group.[1] No patient discontinued the two-year study for reasons of adverse events of the study medication in either group. After 6 months 39 out of the 71 patients who completed this study received suphasalazine as additional antirheumatic therapy on clinical grounds: 20 in the placebo and 19 in the prednisone group.

The use of analgesics and NSAIDs in the prednisone group was about 50% of that of the placebo group as was also the case for the number of local steroid injections and sessions of physiotherapy.[1]

Wellbeing variables (Table 2; Figure 1-5)

Scores of the VDF showed no statistically significant differences (see **Figure 1**). In the items of the scales of the IRGL at 6, 12 and 24 months statistically significant differences between the groups were seen for depressed mood and potential support in favor of the prednisone group; no differences were seen in the other items of the scales (see **Table 2**; **Figure 2,3**). There were statistically significant differences at 3 months in the VAS early morning pain and the VAS general wellbeing between the prednisone group and the placebo group in favor of the prednisone group (see **Figure 4,5**).

TABLE 2

Effect of treatment on IRGL scales of patients with early RA; the prednisone group (pred) versus the placebo group (plac) (means, sem, p-value

		at baseline					at 24 months				
	range	pred	sem	plac	sem	p	pred	sem	Plac	sem	p
Mobility	8-32	21.6	0.6	21.4	0.6	0.09	20.9	0.6	21.5	0.6	0.2
Self care	8-32	25.6	0.5	25.6	0.5	1.0	28.2	0.7	27.0	0.6	0.6
Pain	6-25	14.9	0.4	16.7	0.4	0.09	12.1	0.6	13.5	0.6	0.8
Depressed mood	0-24	3.2	0.5	4.7	0.4	0.02**	3.3	0.4	3.1	0.4	0.06
Cheerful mood	okt-24	10.9	0.5	10.3	0.6	0.5	11.0	0.5	11.6	0.5	0.2
Anxiety	5-20	19.0	0.5	19.6	0.6	0.7	17.9	0.6	17.6	0.5	0.7
Potential support	5-20	14.7	0.4	14.9	0.4	0.9	16.0	0.4	15.5	0.4	0.004**
Actual support	00-xx	6.7	0.2	6.6	0.2	0.8	6.5	0.2	6.8	0.2	1.0
Number of friends	2-8	7.1	0.5	12.4	0.6	0.01**	5.0	0.4	8.1	0.4	0.2
Exchange of visitors	1-4	6.0	0.2	6.0	0.1	0.2	3.0	0.2	3.4	0.2	0.3
Impact on activities	1-4	9.6	0.4	11.4	0.4	0.1	8.5	0.4	9.0	0.4	1.0
Impact on sexuality	1-4	1.6	0.1	1.6	0.1	0.9	3.8	0.2	3.0	0.2	0.2
Impact on eating and sleeping	2-8	2.9	0.2	3.4	0.2	0.2	2.9	0.2	3.4	0.2	1.0
Impact on nutrition/sleep	2-8	2.8	0.2	3.1	0.1	0.4	2.6	0.2	2.7	0.2	0.7
Impact on ADL	1-4	16.8	0.6	19.0	0.6	0.1	15.4	0.6	16.8	0.7	0.7
Impact on relationship partner	1-4	11.7	0.1	15.0	0.1	0.5	1.8	0.8	2.0	0.1	0.2
Impact on family life	1-4	1.5	0.1	1.5	0.1	1.0	6.7	0.5	2.1	0.1	0.4

*p=<0.05 between groups. At 6 months also statistically significant differences between both groups for potential support p=0.03 and at 18 months for depressed mood p= 0.03; data not shown.
**p=<0.05

Disease activity variables

In our study, patients of the prednisone group showed improvement in 8 clinical parameters in the first 3 months compared to the placebo group. The clinical improvement in the prednisone group was transient: after 6 months the only clinical variables showing statistically significant differences were the 28 joint score for tenderness and the grip strength. Most of the clinical variables exhibited no statistically significant differences from baseline between the two groups although the actual improvement was slightly in favor of the prednisone group, reaching statistical significance for the 28 joint score for tenderness (p=0.01). Grip strength improved significantly and consistently in the prednisone group [1]. Thirty-three percent of

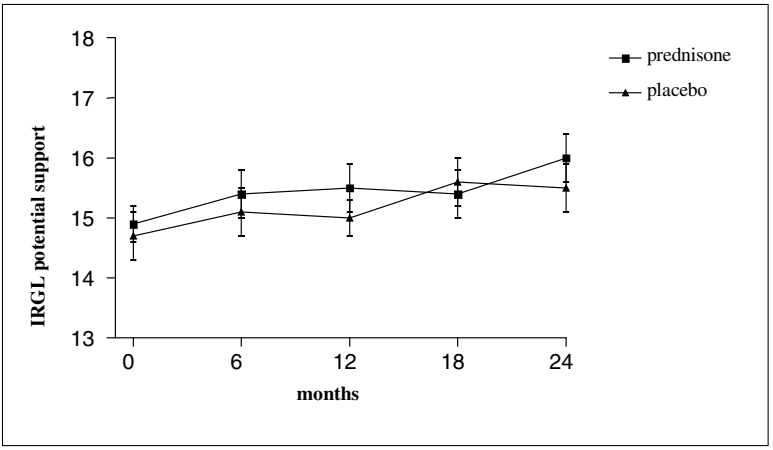


Figure 2. The IRGL scale, potential support of patients with early RA treated with prednisone compared to placebo (means, SEM).
p = 0.05 at 6 months, 0.04 at 12 and 0.004 at 24 month
IRGL Impact of Rheumatic diseases on General health and Lifestyle; mobility, range 7-28, 7 representing the worst score and 28 the best score; self care, range 8-32, 7 representing the worst score and 28 the best score; pain, range 6-25, 6 representing the worst score and 25 the best score.[12]

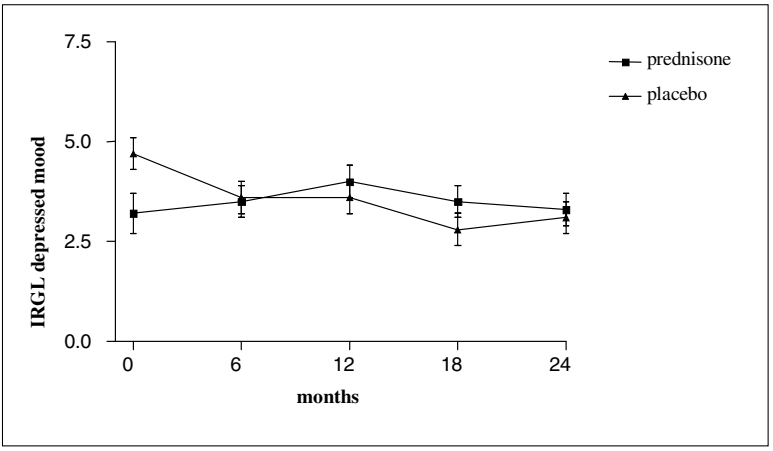


Figure 3. The IRGL scale, depressed mood of patients with early RA treated with prednisone compared to placebo (means, SEM).
p = 0.02 at start and 0.03 at 18 months
IRGL Impact of Rheumatic diseases on General health and Lifestyle; mobility, range 7-28, 7 representing the worst score and 28 the best score; self care, range 8-32, 7 representing the worst score and 28 the best score; pain, range 6-25, 6 representing the worst score and 25 the best score.[12]

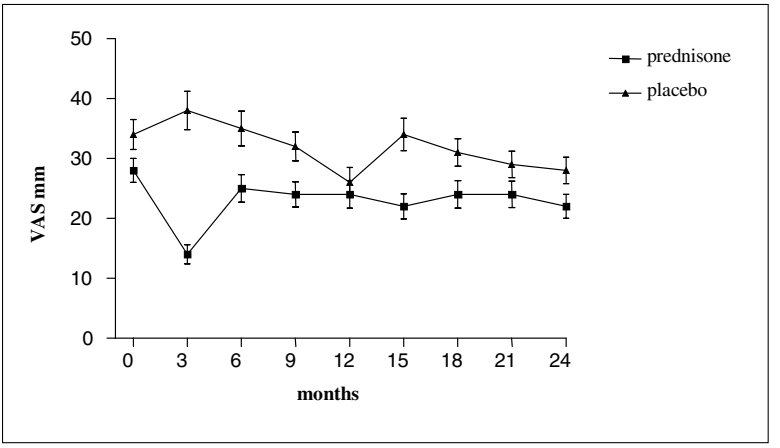


Figure 4. VAS (visual analogue scale) morning pain of patients with early RA treated with prednisone compared to placebo (means, SEM).
p = 0.0003 at 3 months
Visual analogue scale (VAS) of morning pain 0-100 mm., 0 the best score, 100 the worst score.

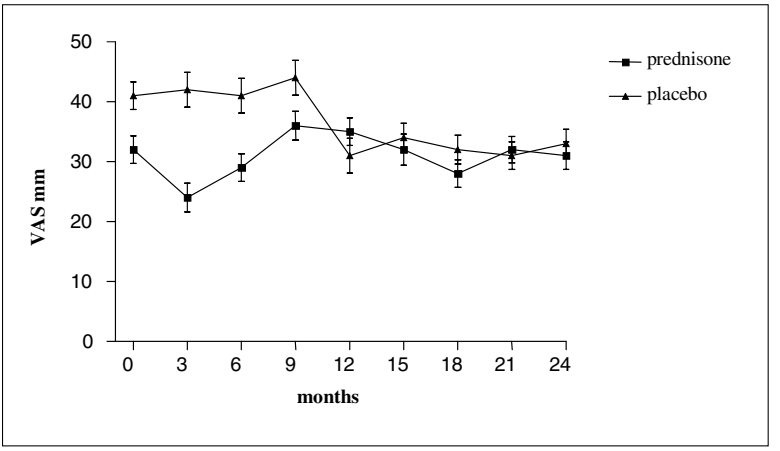


Figure 5. VAS (visual analogue scale) general wellbeing of patients with early RA treated with prednisone compared to placebo (means, SEM).
p = 0.003 at 3 and 0.04 at 6 months
Visual analogue scale (VAS) of general wellbeing 0-100mm, 0 the best score, 100 the worst score.

patients in the prednisone group satisfied the modified 20% ACR individual patient improvement criteria and 24% of patients did in the placebo group at 12 months and 30% and 22%, respectively, at 24 months.

Joint damage

At the start of the study there was no statistically significant difference in joint damage in the prednisone group compared to the placebo group. After one and two years there were statistically significant differences between both groups in favor of the prednisone group,[1] increasing in time.

DISCUSSION

In our study with long term low-dose GC treatment in patients with early active previously untreated RA compared to placebo we found a transient amelioration of disease activity but a significant ongoing reduction in joint damage.[1]

The aim of this study was to investigate general wellbeing in these patients and the role of additional therapies in evaluating the effects of the different treatment strategies. In daily practice GC lead to immediate relief of clinical symptoms and improvement of general wellbeing in patients with RA but relatively little is known about the long term effects on parameters of wellbeing.[17] In the long term, functional disability of patients with RA will be affected not only by current inflammatory activity but also by structural joint damage.[18] In a study comparing disease activity, joint destruction and functional capacity over the course of RA, functional capacity appears to be associated with disease activity in early RA and with joint damage in late disease.[19] In a reappraisal of HAQ-disability in RA as a function of disease over time, the HAQ may be an inadequate model due to the patient's upward reappraisal of functional ability with increasing time.[20]

Over time, we found no enduring differences between the groups for most variables. Scores of the VDF (Dutch version of the HAQ) showed some improvement in the prednisone group, but no statistically significant differences (**Figure 1**). In the domains of the IRGL, 3 items were statistically significantly different in favor of the prednisone group at some points of time (**Figure 2,3**). There was a transient improvement in the VAS early morning pain as well as in the VAS general wellbeing (**Figure 4,5**).

Little is known about the use and effects of additional therapies such as analgesics, NSAIDs, local injections and physiotherapy on aspects of general wellbeing in studies of different therapy strategies in patients with RA. In the present

study the cumulative use of these additional therapies in the prednisone group was 50 % of that in the placebo group. In another study of patients with RA on the effectiveness of early treatment with DMARDs also a doubling of intra-articular injections was found in the first year in the non-DMARD versus the DMARD group (44% vs. 22%).[17] In spite of better disease control, reflected by significant inhibition of joint damage in the prednisone group vs. the placebo group, no difference in wellbeing variables was found, probably due to higher use of additional therapy in the placebo group. The same result was found for clinical disease activity variables.

Therefore, in future clinical drug trials, the use of additional therapies should thus be taken into account analyzing clinical differences in effect; clinical and wellbeing variables not always accurately reflect disease control.

REFERENCES

1. Everdingen AA van, Jacobs JWG, Siewertsz van Reesema DR, Bijlsma JWJ. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease modifying properties and side effects. A double-blind placebo controlled clinical trial. Ann Intern Med 2002;136:1-12.
2. Kirwan JR. Arthritis and Rheumatism Council Low-dose Glucocorticoid study Group: The effect of glucocorticoid on joint destruction in RA. N Engl J Med 1995;333: 142-6.
3. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309-18.
4. Hickling P, Jacoby RK, Kirwan JR and the Arthritis and Rheumatism Council Low Dose Glucocorticoid Study Group. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. Br J Rheumatol 1998;37:930-6.
5. Zeidler H, Rau R, Alkalay I, et al: Efficacy and safety of low-dose prednisolone in early rheumatoid arthritis. Arthritis Rheum 1999;42(Suppl):271 (Abstract).
6. Jacobs JWG, Geenen R, Evers AWM, et al. Short term effects of corticosteroid pulse treatment on disease activity and the wellbeing of patients with active rheumatoid arthritis. Ann Rheum Dis 2001;60:61-4.
7. Schmidt LA, Fox NA, Goldberg MC, et al. Effects of acute prednisone administration on memory, attention and emotion in healthy human adults. Psychoneuroendocrinol 1999;24:461-83.

8. Brown ES, Suppes T. Mood symptoms during corticosteroid therapy: a review. Harv Rev Psychiatry 1998;5:239-46.
9. Booij A, Biewenga-Booij CM, Huber-Bruning O, et al. Androgens as adjuvant treatment in postmenopausal female patients with rheumatoid arthritis. Ann Rheum Dis 1996;55:811-5.
10. Jacobs JWG, Kraaimaat FW, Bijlsma JWJ. Why do patients with rheumatoid arthritis use alternative treatments? Clin Rheumatol 2001;20:192-6.
11. Bijlsma JWJ, Oude Heuvel CHB, Zaalberg A. Development and validation of the Dutch questionnaire capacities of daily life (VDF) for patients with rheumatoid arthritis. J Rehabil Sci 1990;3:71-4.
12. Huiskes CJAE, Kraaimaat FW, Bijlsma JWJ. Development of a self-report questionnaire to assess the impact of rheumatic diseases on health and lifestyle. J Rehabil Sci 1990:3:65-74.
13. Evers AWM, Taal E, Kraaimaat FW, et al. A comparison of two recently developed health status instruments for patients with arthritis: Dutch-AIMS2 and IRGL. Br J Rheumatol 1998;37:157-64.
14. Smolen JS, Breedveld FC, Eberl G, et al. Validity and reliability of the twenty-eight-joint-count for the assessment of rheumatoid arthritis activity. Arthritis Rheum 1995;38:38-44.
15. Prevoo MLL, Riel PLCM van, Hof MA van 't. Validity and reliability of joint indices. A longitudinal study in patients with recent onset rheumatoid arthritis. Br J Rheumatol 1993;32:589-94.
16. Heijde DMFM van der, Riel PLCM van, Leeuwen MA van, et al. Prognostic factors for radiographic damage and physical disability in early rheumatoid arthritis. A prospective follow-up study of 147 patients. Br J Rheumatol 1992;31:519-25.
17. Heide A van der, Jacobs JWG, Dinant HJ, Bijlsma JWJ. The impact of endpoint measures in rheumatoid arthritis clinical trials. Semin Arthritis Rheum 1992;21: 287-94.
18. Heide A van der, Jacobs JWG, Albada-Kuipers GA van, et al. Self report functional disability scores and the use of devices: two distinct aspects of physical function in rheumatoid arthritis. Ann Rheum Dis 1993;52:497-502.
19. Welsing PMJ, Gestel AM van, Swinkels HL, et al. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum 2001;44:2009-117.
20. Wolfe F. A reappraisal of HAQ disability in rheumatoid arthritis. Arthritis Rheum 2000;43:2751-61.

Down regulation of glucocorticoid receptors in early-diagnosed rheumatoid arthritis

CHAPTER 5

AA van Everdingen
AM Huisman
MJG Wenting
DR Siewertsz van Reesema
JWG Jacobs
JWJ Bijlsma

Clinical and Experimental Rheumatology

Abstract

Objective

In patients with rheumatoid arthritis (RA) of longer duration, glucocorticoid receptor (GR) down-regulation has been reported, without change in cortisol levels. This phenomenon might play a role in the aetio-pathogenesis of RA. Therefore we studied the GR-expression, as well as the serum cortisol levels in patients with recently diagnosed RA.

Methods

In 81 early diagnosed RA patients with disease duration < 1 year (52F/29M; mean (SD) age 63(13) years) and in 39 age and sex matched controls (23F/16M;mean age 63(15) years) blood samples were taken between 8-10h AM. GR-expression (GR-number and GR-affinity), serum cortisol levels, ESR, CRP, painful and swollen joints were measured.

Results

A significantly lower GR-number was found in the female patients compared with female controls: 7.0 versus 9.8 fmol/million cells, respectively (difference: 2.8, 95% CI 1.1 – 4.6). Interestingly, also serum cortisol levels were significantly lower in the female patients compared with the female controls: 0.21 versus 0.41 μmol/l, respectively (difference: 0.20, 95% CI 0.12 – 0.28). However, between the male patients and male controls, no difference was found, in GR-expression nor in serum cortisol levels. Neither in female nor in male patients correlations were found of GR-expression with parameters of disease activity nor was there a relation between GR-expression and serum cortisol levels.

Conclusion

Changes in GR-expression as well as serum cortisol were not a general phenomenon in early diagnosed RA patients, being only present in females and not related to disease activity. Therefore it seems unlikely that GR-expression per se is causally involved in the pathogenesis of RA. We cannot preclude that it may be involved in the incidence, severity and course of RA, as this may be differentially regulated in males and females.

INTRODUCTION

Glucocorticoids are being successfully used in the treatment of early rheumatoid arthritis (RA) because of their potent anti-inflammatory action. Not all patients do respond however and if so, some patients respond to low doses, while others require larger doses for seemingly identical clinical situations. Glucocorticoids exert their effects through the glucocorticoid receptor (GR) located in the cytoplasm of target cells at low doses,[1,2] but at higher doses genomic (i.e. through the GR) as well as non-genomic modes of action play a role.[3] It is known that the number of intracellular GRs per cell is closely related to the biological response upon glucocorticoid exposure to that cell.[4] In this context the GR expression of peripheral mononuclear cells (PBMC) is considered to reflect in vivo biological effects of glucocorticoids in healthy persons and in a variety of disorders.[5-9] GR in normal leukocytes do not show significant alterations within a day, in contrast to plasma cortisol levels.[5] GR down regulation might hinder the effectiveness of the immune-hypothalamic- pituitary-adrenal axis in the control of inflammation and therefore might play a role in the aetio-pathogenesis of RA.[6,10]

Schlaghecke et al. showed a diminished GR-number per cell in mononuclear leukocytes of RA patients with active disease of longer duration (mean 6 years) compared with healthy controls.[6,11] There were no differences in GR binding affinity or serum cortisol levels. No correlation was found between GR-number and age or sex, RA activity or serum cortisol. The decrease in GR-number in RA is compatible with impaired activity of the hypothalamic-pituitary-adrenal (HPA) axis.[10,12,13] The diminished receptor density in RA patients did not result in glucocorticoid resistance in the sense that proliferation and cytokine release (interleukine 1 and 6) of lymphocytes of RA patients and healthy controls were inhibited by glucocorticoids to the same extent.[11] This study was done with relatively high glucocorticoid doses: adding glucocorticoids to PBMC, acting by GR, but probably also by the qualitatively quite different non-genomic (i.e. not GR related) effects of glucocorticoids.[3] In contrast to the diminished GRs in active RA patients, Sanden et al. showed in patients with rheumatic diseases an overall increase in the number of GRs compared with healthy controls. However, patients in this study had a variety of different rheumatic diseases with a large range in disease activity. The increased number of GRs decreased on glucocorticoid therapy in a dose-dependent way.[14]

If GR-downregulation plays a role in the aetio-pathogenesis of RA a diminished GR-number would not only be found in RA of longer duration,[6] but especially in early-diagnosed RA. To investigate this hypothesis, we compared the GR-expression as well as the serumcortisol levels of early RA-patients with those of age-and sex-matched healthy controls.

PATIENTS AND METHODS

Patients

Eighty-one consecutive outpatients with recently diagnosed (early) RA (disease duration < 1 year) were included. All patients fulfilled the ACR criteria and were DMARD and glucocorticoid naive. 68% of the RA patients (55 out of 81) used non steroidal anti-inflammatory drugs (NSAID's) and 74% (60 out of 81) were IgMRF positive. Age varied between 24 and 82 years with a mean (SD) age of 63(13) years. The cohort consisted of 29 males (age 61(12) years) and 52 females (age 64(13)). From these patients disease activity (ESR, CRP, number of tender and swollen joints) and serum cortisol levels were determined. From the last 50 included patients glucocorticoid receptor (GR) density and affinity were determined as well. This sub-population had a similar mean age (64(12) years) and age distribution (varying from 29 to 82 years) as the entire group. Also the male / female ratio (19 / 31), and age distribution between both sexes (male 63(13); female 65(12)) were similar to the entire group. In addition, cortisol, GR-density and -affinity were determined from an age and sex matched group of healthy individuals. This group included 39 individuals with a mean age of 63(15) years: 16 males (61(12) years) and 23 females (62(16) years).

Assays

Swollen and tender joints were scored as has been described.[15] Blood samples were collected between 8:00 and 10:00 AM. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were determined according to standard procedures. Serum cortisol levels were determined using a fluorescence polarisation immuno-assay (FPIA; Abbot, Illinois, USA) according to manufacturer instructions. The inter-assay coefficients of variation were 4.6, 3.3 and 3.8% at serum concentrations of 0.29, 0.47 and 0.81 μmol/l, respectively (n=54, 54 and 24).

GR density and affinity in PBMC were determined as follows: PBMC were isolated from 40 ml (EDTA) blood using Ficoll-paque density centrifugation.[16-19]

The cell suspension was stored overnight at 4°C in Iscove's medium supplemented with 10% foetal bovine serum that was absorbed with dextran-coated charcoal to remove free steroid.[20] PBMC were centrifugated and washed 2 times with Hanks balanced salt solution HBSS (without calcium or magnesium; with 3.6 mM $NaHCO_3$, pH7.2, 4°C). Trypan blue staining revealed ≥95% viable cells. A binding curve was made in duplicate by adding 100 µl ^{3}H-dexamethasone in 7 concentrations (1.25-40 nM Amersham; 3.18 TBq/mmol) to 1-2 x10^6 cells per 100 µl. At the end of the incubation period (at 24°C with rotation for 90 min), cells were washed 3 times with 20 mM sodium molybdate dihydrate in HBSS to stabilise receptor-ligand binding,[21] followed by quantification of the bound ^{3}H-dexamethasone using scintillation analysis. The maximum ^{3}H-dexamethasone binding based on scatchard analysis[22,23] revealed the number of unoccupied GRs expressed in fmol/million cells, recalculated in absolute number of receptors per cell. The slope of the line in scatchard analysis reflects the GR binding affinity (Kd) expressed in nM.

Statistical evaluation

For comparison between groups, unpaired two-sided student's T-tests or Mann-Whitney U tests were used, where appropriate. In addition, multiple regression analysis was done. Correlations, Spearman or Pearson coefficients, where appropriate, were calculated between the different parameters. Statistical significance was defined at $P < 0.05$. Data are expressed as mean ± SEM.

RESULTS

First the results are described of the whole group (**Figures 1a**, **1b** and **1c**) and then those of women and men separately (**Figures 2a**, **2b** and **2c**). **Figure 1a** shows the serum cortisol levels of the RA patients compared with healthy controls. In this recently diagnosed RA population a statistically significantly lower serum cortisol level was found compared to the controls (35% lower, $p \leq 0.001$). Multiple regression analysis showed that age was not responsible for the difference in serum cortisol levels between the RA cohort and the healthy controls. GR receptor numbers (**Figure 1b**) were also statistically significantly lower (on average almost 20 %, $p<0.02$) in these early RA patients compared with the controls. Again, age was not responsible for this difference. Mean GR-affinity was slightly lower in the early RA patients compared with the age and sex matched control group but no statistically significant difference was obtained (**Figure 1c**).

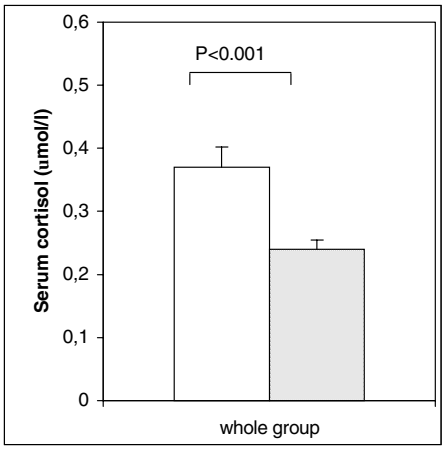


Figure 1a. Serum cortisol levels (µmol/l) of the healthy controls (open bars) compared with early-RA patients (gray bars). Values total control group 0.37(0.03). Values total early-RA group 0.24(0.015). Mean values (SEM).

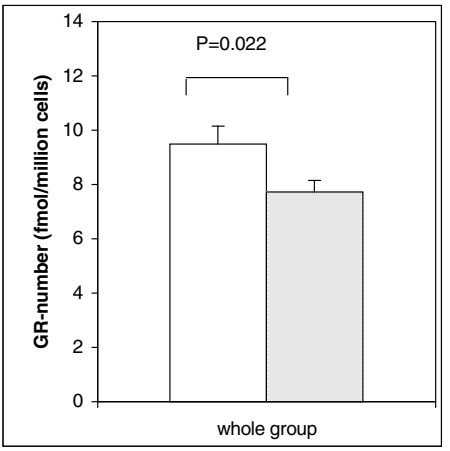


Figure 1b. GR-number: fmol/million cells. The open bars represent the healthy control group and the gray bars the early-RA group. Values total control group 9.48(0.66). Values total RA group 7.73(0.41). Mean values (SEM).

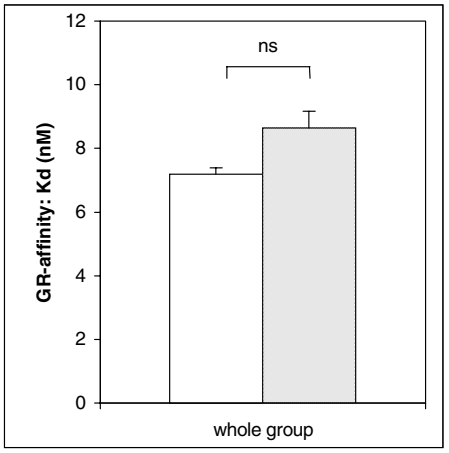


Figure 1c. GR-affinity (Kd) expressed in nM. The open bars represent the healthy control group and the gray bars the early-RA group. Values total control group 7.19(0.48). Values total RA group 8.64(0.53). Mean values (SEM).

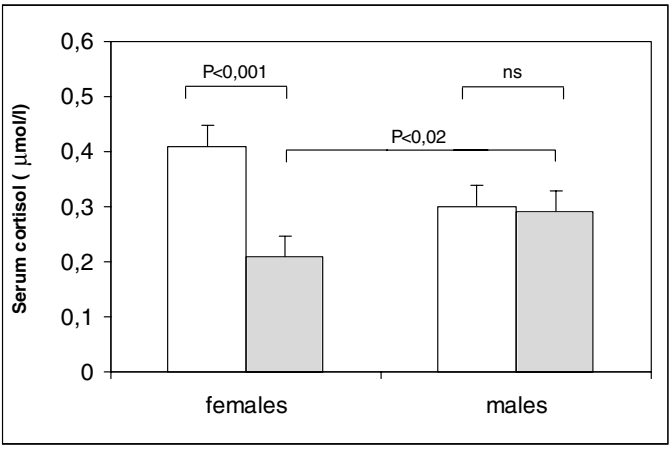


Figure 2a. Serum cortisol levels (µmol/l) of the healthy female controls (open bars) compared with female early-RA group (gray bars). Values female control group: 0.41(0.05) and female early-RA group 0.21(0.02). Values male control group: 0.30(0.035) and male early-RA group 0.29(0.03). Mean values (SEM).

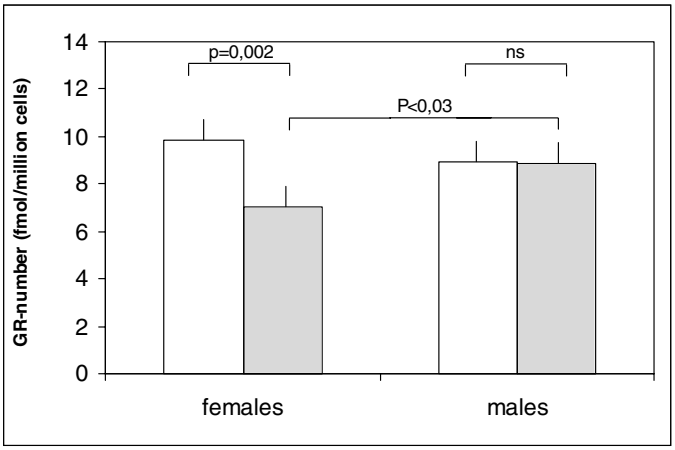


Figure 2b. GR-number: fmol/million cells. The open bars represent the healthy control group and the gray bars the early-RA group. Values female control group: 9.84(0.79) and female early-RA group: 7.03(0.47). Values male control group: 8.92(0.35) and male early-RA group 8.88(0.71). Mean values (SEM).

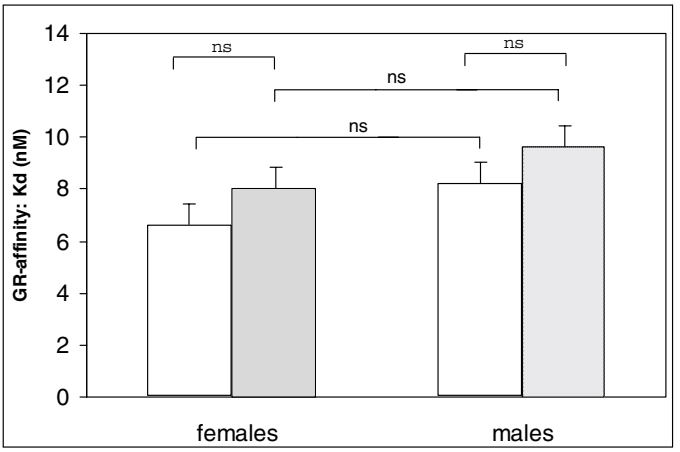


Figure 2c. GR-affinity (Kd) in nM. The open bars represent the healthy control group and the gray bars the early-RA group. Values female control group 6.53(0.44) and female early-RA group: 8.02(0.57). Values male control group: 8.18(0.29) and male early-RA group 9.64(1.02). Mean values (SEM).

Serum cortisol levels, GR number and affinity did not correlate with age, neither in the controls, nor in the early RA group. For patients and controls together there was a positive correlation between GR number and receptor affinity (correlation coefficient 0.45, $p \leq 0.001$). No correlations of the GR parameters with serum cortisol were found.
With respect to parameters of disease activity in the RA group, there were no correlations of serum cortisol, GR-number or GR-affinity with ESR (mean 31 ± 3 mm/1st hour), CRP (mean 16 ± 3 mg/L), swollen joints (mean number 8.0 ± 0.4) or tender joints (mean number 8.7 ± 0.6).

Surprisingly, the differences between the RA patients and the healthy controls were almost entirely determined by the female patients. Significantly lower serum cortisol levels were found in the female patients compared with female controls (0.21 versus 0.41 µmol/l; difference 0,20, 95% CI 0.12 – 0.28) (**Figure 2a**). Between the male patients and male controls serum cortisol levels were not different. The serum cortisol levels in controls were higher (although not statistically significant) in females than in the males, but female RA patients had a lower serum cortisol level than the male patients (28% lower, $p \leq 0.02$).

Similar observations were found for the GR number. The female patients determined the difference between the RA patients and controls. A significantly lower GR-number was found in the female patients compared with female controls (7.0 versus 9.8 fmol/million cells; difference 2.8, 95% CI 1.1 – 4.6) (**Figure 2b**). For males no differences were found in GR number between early RA patients and controls. The GR-number was not statistically different between male and female controls but in RA females they were lower than in the RA males (21% lower, $p \leq 0.03$).

The GR affinity showed a negative trend for both sexes: the Kd being higher means that the affinity is lower in the early RA patients compared with controls. These differences were not statistically significant (**Figures 1c** and **2c**).

DISCUSSION

In our group of early RA patients a significantly lower serum cortisol and GR number was found in the patients compared with controls. These findings suggest that glucocorticoid control of inflammation may be impaired in early RA patients. This is in agreement with the studies of Schlaghecke (adult RA patients with longer disease duration)[6] and Andreae (children with autoimmune diseases, two thirds of them suffering from juvenile idiopathic arthritis).[24] The lower serum cortisol and GR number could completely be attributed to the female patients, since no differences were observed between the male patients and their controls. The GR-affinity tended to be lower in the patients compared with controls (**Figures 1c** and **2c**). However, this was not statistically significant. No correlations were found between GR-number and parameters of disease activity, nor was there a relation between GR-number and serum-cortisol levels. However, disease activity determined by ESR, CRP, painful and swollen joints was rather low, so it was less likely to find correlations.

Different studies show different outcomes with respect to early morning cortisol levels in RA.[25-27] Neeck et al. show for active RA patients increased serum cortisol levels and disappearance of cortisol circadian rhythm.[25] Their RA patients had a much higher disease activity than our early RA patients. In patients with recent onset RA the dynamic cortisol responsiveness as reflected in the early morning rise is not disturbed.[27] The studies of Neeck and Dekkers are in contrast to the results of the study of van den Brink[28] and our study in which decreased morning serum cortisol levels in postmenopausal RA patients are found, reflecting a relative hypocortisolism. Above mentioned discrepancies might be attributed to differences in disease activity and disease duration, but also to the time of blood sampling,

which is ideal at the moment of awakening. Patients in our study first had to travel at least an hour before blood could be sampled between 8 – 10 AM; immediate saliva sampling after awakening by the patient him or herself would have been better.

Another way to study the HPA-axis in RA might be with an overnight dexamethasone suppression test with a dose as low as 0.25 mg dexamethasone instead of 1 mg. In case of relative hypercortisolism in early RA, differences might be observed in suppressibility of the HPA-axis with an adjusted dexamethasone suppression test of 0.25 mg.[29] One mg dexamethasone might be a too high dose to allow the detection of subtle individual differences in sensitivity of the HPA-axis to glucocorticoids.

In RA patients with a mean disease duration of six years, GR-downregulation has been reported without change in serum cortisol levels and without correlations between GR-number and age or sex, RA-activity or serum cortisol levels.[6,11] In our early female RA patients a decrease in GR number was found as well a decrease in serum cortisol levels. This was not the case in the early diagnosed male RA patients. The discrepancy with the studies of Schlaghecke might be due to the fact that the populations differ in time of onset of disease, disease activity and time of blood sampling after awakening.[6,11] The sex difference found in our study, the GR-downregulation and lower serum cortisol levels being present in the early diagnosed female RA patients but not in the early diagnosed male RA patients might be related to interactions of sex hormones and the HPA-axis.[2,30,31] The majority of patients suffering from RA are females, suggesting that the balance between androgens and estrogens plays a role in susceptibility of RA.[31,32] The depressive effects of androgens on the immune system might protect males against RA.[30,31] In addition androgens are considered as adjuvant therapy for men and postmenopausal women with RA, having anabolic and slightly disease modifying effects.[33-36] Estrogens and androgens have been shown to affect the GR expression in the central nervous system.[30] Estrogens decrease the expression of GRs in the anterior pituitary, hypothalamus and hippocampus of gonadectomized female rats, whereas androgens have the opposite effect upon GR expression in the medial pre-optic area of orchidectomized male rats.[37-40] The possibility that similar interactions may occur in peripheral mononuclear cells opens interesting perspectives into our results, especially taking into account that male RA is associated with diminished serum androgen levels.

In conclusion: GR-down regulation is not a general phenomenon; it is only present in (especially postmenopausal) females but not in males. That makes it less likely that GR-down regulation plays a major role per se in the aetio-pathogenesis of RA. However, it might be a co-factor, determining the difference in incidence of RA, being less prevalent in males than in females and determining the difference in the severity and course of the disease and its response to glucocorticoid therapy. In addition the question arises if GR expression is different in pre versus post menopausal patients.

REFERENCES

1. Adcock IM, Nasuhara Y, Stevens DA, Barnes PJ. Ligand-induced differentiation of glucocorticoid receptor (GR) trans-repression and transactivation: preferential targetting of NF-kappaB and lack of I-kappaB involvement. Br J Pharmacol 1999; 127:1003-1011.
2. Da Silva JA, Bijlsma JW. Optimizing glucocorticoid therapy in rheumatoid arthritis. Rheum Dis Clin North Am 2000; 26:859-880.
3. Buttgereit F, Wehling M, Burmester GR. A new hypothesis of modular glucocorticoid actions: steroid treatment of rheumatic diseases revisited. Arthritis Rheum 1998; 41:761-767.
4. Vanderbilt JN, Miesfeld R, Maler BA, Yamamoto KR. Intracellular receptor concentration limits glucocorticoid-dependent enhancer activity. Mol Endocrinol 1987; 1:68-74.
5. Tanaka H, Akama H, Ichikawa Y, Homma M, Oshima H. Glucocorticoid receptors in normal leukocytes: effects of age, gender, season, and plasma cortisol concentrations. Clin Chem 1991; 37:1715-1719.
6. Schlaghecke R, Kornely E, Wollenhaupt J, Specker C. Glucocorticoid receptors in rheumatoid arthritis. Arthritis Rheum 1992; 35:740-744.
7. Norbiato G, Bevilacqua M, Vago T, Baldi G, Chebat E, Bertora P, et al. Cortisol resistance in acquired immunodeficiency syndrome. J Clin Endocrinol Metab 1992; 74:608-613.
8. Invitti C, Redaelli G, Baldi G, Cavagnini F. Glucocorticoid receptors in anorexia nervosa and Cushing's disease. Biol Psychiatry 1999; 45:1467-1471.
9. Armanini D, Spinella P, Simoncini M, Basso A, Zovato S, Pozzan GB, et al. Regulation of corticosteroid receptors in patients with anorexia nervosa and Cushing's syndrome. J Endocrinol 1998; 158:435-439.

10. Straub RH, Cutolo M. Involvement of the hypothalamic-pituitary-adrenal/gonadal axis and the peripheral nervous system in rheumatoid arthritis: viewpoint based on a systemic pathogenetic role. Arthritis Rheum 2001; 44:493-507.
11. Schlaghecke R, Beuscher D, Kornely E, Specker C. Effects of glucocorticoids in rheumatoid arthritis. Diminished glucocorticoid receptors do not result in glucocorticoid resistance. Arthritis Rheum 1994; 37:1127-1131.
12. Gudbjornsson B, Skogseid B, Oberg K, Wide L, Hallgren R. Intact adrenocorticotropic hormone secretion but impaired cortisol response in patients with active rheumatoid arthritis. Effect of glucocorticoids. J Rheumatol 1996; 23:596-602.
13. Masi AT, Chrousos GP. Hypothalamic-pituitary-adrenal-glucocorticoid axis function in rheumatoid arthritis. J Rheumatol 1996; 23:577-581.
14. Sanden S, Tripmacher R, Weltrich R, Rohde W, Hiepe F, Burmester GR, et al. Glucocorticoid dose dependent downregulation of glucocorticoid receptors in patients with rheumatic diseases. J Rheumatol 2000; 27:1265-1270.
15. Fuchs HA, Pincus T. Reduced joint counts in controlled clinical trials in rheumatoid arthritis. Arthritis Rheum 1994; 37:470-475.
16. Boyum A. Isolation of mononuclear cells and granulocytes from human blood. Isolation of monuclear cells by one centrifugation, and of granulocytes by combining centrifugation and sedimentation at 1 g. Scand J Clin Lab Invest Suppl 1968; 97:77-89.
17. Costlow ME, Pui CH, Dahl GV. Glucocorticoid receptors in childhood acute lymphocytic leukemia. Cancer Res 1982; 42:4801-4806.
18. Steiner AE, Wittliff JL. A whole-cell assay for glucocorticoid binding sites in normal human lymphocytes. Clin Chem 1985; 31:1855-1860.
19. Wenting-Van Wijk MJ, Blankenstein MA, Lafeber FP, Bijlsma JW. Relation of plasma dexamethasone to clinical response. Clin Exp Rheumatol 1999; 17:305-312.
20. Papamichail M, Ioannidis C, Tsawdaroglou N, Sekeris CE. Translocation of glucocorticoid receptor from the cytoplasm into the nucleus of phytohemagglutinin-stimulated human lymphocytes in the absence of the hormone. Exp Cell Res 1981; 133:461-465.
21. Leach KL, Dahmer MK, Hammond ND, Sando JJ, Pratt WB. Molybdate inhibition of glucocorticoid receptor inactivation and transformation. J Biol Chem 1979; 254:11884-11890.
22. Scatchard G. The attraction of proteins for small molecules and ions. NY Acad Sci 1949; 51:660-672.
23. Lippman M, Barr R. Glucocorticoid receptors in purified subpopulations of human peripheral blood lymphocytes. J Immunol 1977; 118:1977-1981.

24. Andreae J, Tripmacher R, Weltrich R, Rohde W, Keitzer R, Wahn U, et al. Effect of glucocorticoid therapy on glucocorticoid receptors in children with autoimmune diseases. Pediatr Res 2001; 49:130-135.
25. Neeck G, Federlin K, Graef V, Rusch D, Schmidt KL. Adrenal secretion of cortisol in patients with rheumatoid arthritis. J Rheumatol 1990; 17:24-29.
26. Mirone L, Altomonte L, D'Agostino P, Zoli A, Barini A, Magaro M. A study of serum androgen and cortisol levels in female patients with rheumatoid arthritis. Correlation with disease activity. Clin Rheumatol 1996; 15:15-19.
27. Dekkers JC, Geenen R, Godaert GL, van Doornen LJ, Bijlsma JW. Diurnal rhythm of salivary cortisol levels in patients with recent-onset rheumatoid arthritis. Arthritis Rheum 2000; 43:465-467.
28. van den Brink HR, Blankenstein MA, Koppeschaar HP, Bijlsma JW. Influence of disease activity on steroid hormone levels in peripheral blood of patients with rheumatoid arthritis. Clin Exp Rheumatol 1993; 11:649-652.
29. Huizenga NA, Koper JW, De Lange P, Pols HA, Stolk RP, Burger H, et al. A polymorphism in the glucocorticoid receptor gene may be associated with and increased sensitivity to glucocorticoids in vivo. J Clin Endocrinol Metab 1998; 83:144-151.
30. Da Silva JA. Sex hormones and glucocorticoids: interactions with the immune system. Ann N Y Acad Sci 1999; 876:102-117.
31. Cutolo M, Sulli A, Villaggio B, Seriolo B, Accardo S. Relations between steroid hormones and cytokines in rheumatoid arthritis and systemic lupus erythematosus. Ann Rheum Dis 1998; 57:573-577.
32. Cutolo M, Wilder RL. Different roles for androgens and estrogens in the susceptibility to autoimmune rheumatic diseases. Rheum Dis Clin North Am 2000; 26:825-839.
33. 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.
34. Booij A, Biewenga-Booij CM, Huber-Bruning O, Cornelis C, Jacobs JW, Bijlsma JW. Androgens as adjuvant treatment in postmenopausal female patients with rheumatoid arthritis. Ann Rheum Dis 1996; 55:811-815.
35. Bijlsma JW. Can we use steroid hormones to immunomodulate rheumatic diseases? Rheumatoid arthritis as an example. Ann N Y Acad Sci 1999; 876:366-376.
36. Hall GM, Larbre JP, Spector TD, Perry LA, Da Silva JA. A randomized trial of testosterone therapy in males with rheumatoid arthritis. Br J Rheumatol 1996; 35:568-573.

37. Burgess LH, Handa RJ. Estrogen-induced alterartions in the regulation of mineralocorticoid and glucocorticoid messenger RNA expression in the female rat anterior pituitary gland and brain. Mol Cell Neurosci 1993; 4:191-198.
38. Turner BB. Sex differences in the binding of type I and type II corticosteroid receptors in rat hippocampus. Brain Res 1992; 581:229-236.
39. Carey MP, Deterd CH, de Koning J, Helmerhorst F, de Kloet ER. The influence of ovarian steroids on hypothalamic-pituitary-adrenal regulation in the female rat. J Endocrinol 1995; 144:311-321.
40. Viau V, Meaney MJ. The inhibitory effect of testosterone on hypothalamic-pituitary-adrenal responses to stress is mediated by the medial preoptic area. J Neurosci 1996; 16:1866-1876.

Glucocorticoid receptor up-regulation in early rheumatoid arthritis upon low dose prednisone and placebo

CHAPTER 6

AM Huisman
AA van Everdingen
MJG Wenting
F Lafeber
DR Siewertsz van Reesema
JWG Jacobs
JWJ Bijlsma

Clinical and Experimental Rheumatology

Abstract

Objective

Low or medium dose prednisone in early rheumatoid arthritis (RA), although with significant variation in clinical efficacy, reduces the progression of joint damage. The glucocorticoid receptor (GR) number of peripheral mononuclear cells (PBMC) might be helpful to predict which patients will respond upon low or medium dose prednisone and which patients do not or will need higher doses. Therefore we determined in a double blind placebo controlled study at baseline and yearly the GR-number in PBMC.

Methods

Eighty-one early RA-patients (disease duration < one year) were included. All patients fulfilled the ACR criteria and were disease modifying antirheumatic drugs (DMARD) and glucocortoid-naive. They were randomly assigned to treatment with 10 mg prednisone daily or placebo. From all patients disease activity (CRP, number of tender and swollen joints), radiological joint score, bone mineral density and GR-number in PBMC were measured yearly.

Results

In females the GR-number is up-regulated in time, both in the prednisone as well as in the placebo group.The same trend was observed in males. No correlations were found between the GR-number in the prednisone users at the start of their treatment and change of radiological scores or bone density after two years of treatment. No correlations were found between the GR-number at the start and the clinical characteristics after follow-up of two years.

Conclusion

The GR-number of PBMC of early RA patients could not predict which patients were going to be prednisone responders based on clinical or radiological parameters. However, the up-regulation of GR-number of PBMC in early RA patients towards the GR-number of healthy subjects during the first two years of their disease course seems to reflect a recovery or a compensatory mechanism as an answer upon an ongoing inflammatory process. This recovery might be not enough to efficiently control the inflammatory situation.

INTRODUCTION

Glucocorticoid receptors (GR) are down regulated in rheumatoid arthritis (RA), in early as well as in long standing disease.[1-3] This might reflect an impaired activity of the hypothalamic-pituitary-adrenal(HPA) axis, and thus play a role in the aetiopathogenesis of RA.[4] Recently, relatively low levels of ACTH and cortisol were found in relation to Il-6 and TNF in early RA compared with healthy controls.[5-7] Therefore, this could be an argument to prescribe glucocorticoids to RA patients in order to compensate the relative insufficient HPA-axis. Moreover, recent studies showed that glucocorticoids reduced the progression of joint damage in monotherapy (10 mg prednisone),[8] as well as in combination therapy with disease-modifying anti-rheumatic drugs (DMARDs).[9-11] Biological effects of glucocorticoids at low and medium doses are mediated by the intracellular GR located in the cytoplasm of target cells[12,13] and the number of intracellular GRs per cell is closely related to the biological response of glucocorticoids.[14] Low dose prednisone is defined as 7.5 mg prednisone equivalents daily or less and medium dose as > 7.5mg, but ≤ 30 mg prednisone daily.[15] Clinically, not all patients do respond in the same way: some patients respond to low doses, while others require higher doses for seemingly identical clinical situations. The question is whether the number of GR of peripheral mononuclear cells (PBMC) might be helpful to predict which patient will be responder upon low or medium dose prednisone and which patient needs higher doses. In this context it is of interest to mention that in lupus patients suffering from nephrotic syndrome, a distinct relation of GR level was observed on the clinical responsiveness with glucocorticoid therapy: improved and recovered patients have higher GR-number after glucocorticoid therapy than unimproved patients.[16] The authors speculate that patients with relative higher GR-number are more susceptible to glucocorticoids. Steroid resistant asthma patients also show abnormalities of GR-expression: steroid resistant patients have lower GR-number and GR-affinity than steroid sensitive patients.[17] The aim of this study is to determine at baseline, but also yearly the GR-number in PBMC upon 10 mg prednisone therapy as well as upon placebo. The question is: do the early RA patients with higher GR-number respond better to 10 mg prednisone daily than the patients with a lower GR-number?

MATERIAL AND METHODS

Patients

Eighty-one consecutive out-patients with recently diagnosed RA (disease duration<1 year) were included. All patients fulfilled the ACR criteria for RA and were DMARD and glucocorticoid naive. They were randomly assigned, in blocks of 10, to one of two treatment groups. One group received 10 mg prednisone daily and one group placebo. The code of randomisation was broken after 2 years of treatment and then the prednisone dosage was tapered. Patients were allowed to use non-steroidal anti-inflammatory drugs (NSAIDs)on demand. After 6 months, sulfasalazine (2 gram/day) could be prescribed as rescue medication. The decision to add sulfasalazine was made on clinical grounds (activity of RA). Patient characteristics were as follows: age varied between 24 and 82 years with a mean (±SD) age of 63 ±13 years. The cohort consisted of 29 males (age 61 ±12) years and 52 females (age 64 ±13 years). Age and sex was equally distributed over the treatment and placebo groups, as well as IgM rheumatic factor and the number of patients with erosive disease. From all patients disease activity (CRP, number of tender and swollen joints), radiological joint score (joint erosion and joint narrowing score), bone mineral density and GR-number in PBMC were measured yearly.

Assays

Tender and swollen joints were scored as has been described.[18] Blood samples were collected between 8.00 and 10.00 AM. CRP was determined according to standard procedures. GR-number was determined as follows: PBMC were isolated from 40 ml (EDTA) blood using Ficoll-paque density centrifugation.[19-22] The cell suspension was stored overnight at 4°C in Iscove's medium supplemented with 10% foetal bovine serum that was absorbed with dextran-coated charcoal to remove free steroid.[23] PBMC were centrifugated and washed 2 times with Hanks balanced salt solution HBSS (without calcium or magnesium; with 3.6 mM $NaHCO_3$, pH7.2, 4°C). Trypan blue staining revealed ≥95% viable cells. A binding curve was made in duplicate by adding 100 µl ^{3}H-dexamethasone in 7 concentrations (1.25-40 nM Amersham; 3.18 TBq/mmol) to 1-2 x10^6 cells per 100 µl. At the end of the incubation period (at 24°C with rotation for 90 min), cells were washed 3 times with 20 mM sodium molybdate dihydrate in HBSS to stabilise receptor-ligand binding,[24] followed by quantification of the bound ^{3}H-dexamethasone using scintillation analysis. The maximum ^{3}H-dexamethasone binding based on scatchard analysis[25,26] revealed the

number of unoccupied GRs expressed in fmol/million cells, recalculated in absolute number of receptors per cell. The slope of the line in scatchard analysis reflects the GR binding affinity(Kd) expressed in nM.

Statistical evaluation

All statistical analyses evaluating the effect of treatment were performed according to the intention-to-treat- principle. For the 10 patients (4 in the prednisone group and 6 in the treatment group) who withdrew during the study, the outcomes of the last measurements were carried forward, with the exception of the radiologic scores. For comparison between groups, unpaired two-sided Student s T-tests or Mann-Whitney U tests were used, where appropriate. Statistical significance was defined at $p<0.05$. Data are expressed as mean ± SEM. Analyses were performed with the Number Cruncher Statistical System 97(NCSS Statistical Software, Kaysville, Utah).

RESULTS

Both in females and in males the GR-number increased in time, both in the prednisone as well as in the placebo group (**Figure 1**). However, only in females it reaches statistical significance: the GR-number of female prednisone users at t=2 years versus t=0 years: 10.2 vs. 7.5 fmol/10^6 cells ($p_{Mann\text{-}Withney\text{-}U} = 0.043$), the GR-number of female placebo patients at t=2 years versus t=0 years: 11.0 vs. 6.7 fmol/10^6 cells ($p_{Mann\text{-}Withney\text{-}U} = 0.000$). Leucocytosis did not occur after 1 or 2 years of treatment with prednisone nor a significant rise of lymphocytes or monocytes. GR affinity(Kd) after 2 years of treatment was in the female placebo patients significantly higher compared with the level at base line. No differences in GR affinity were observed in the female prednisone users nor in the male patients. CRP and the number of tender joints did not change significantly in the follow-up years. The number of swollen joints decreased significantly in the follow-up years. This illustrates that the disease activity, which at t=0 was moderate with a mean CRP of 14.2 (3.3) mg/ml in the female patients and 18.5 (4.8) mg/ml in the male patients, remained about the same during the follow-up years. No correlations were found between the GR-number in the prednisone users at t=0 and changes in radiological scores during 2 years of treatment. Neither a correlation was found with changes in BMD after 2 years. However, 4 prednison users developed osteoporotic vertebral fractures.

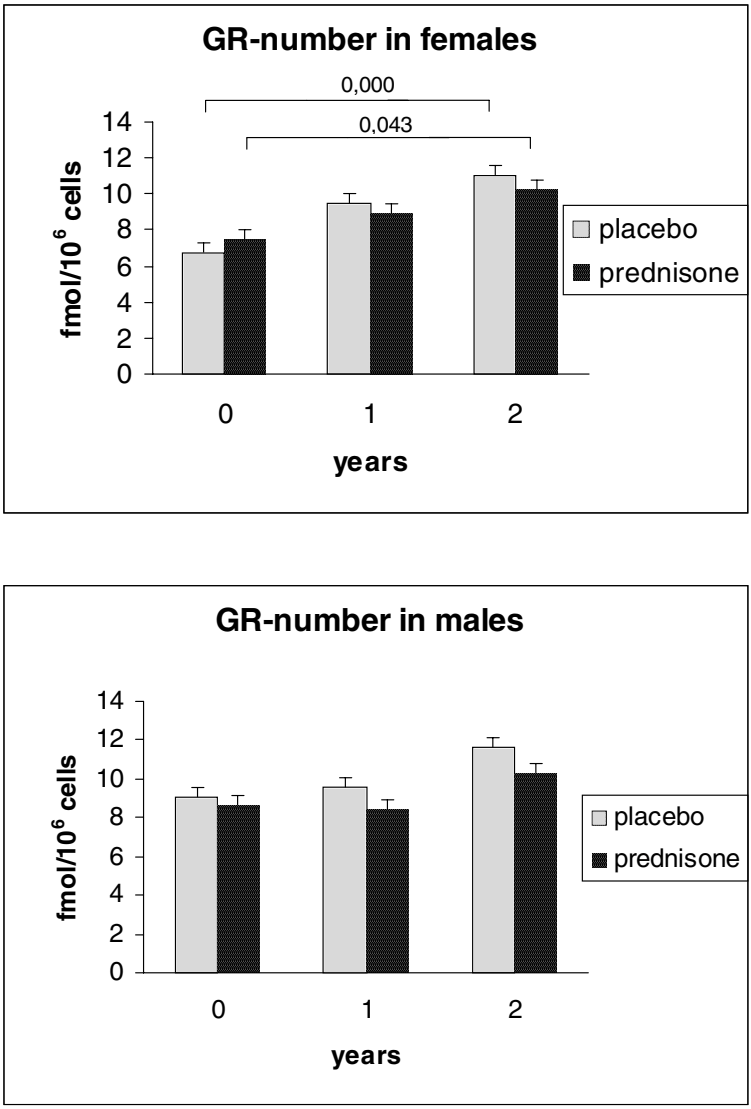


Figure 1. GR-number in PBMC in female (upper panel) and male (lower panel) RA patients treated with 10 mg prednisone daily or placebo. At time (t) = 0 patients were not yet treated. At t = 1 and t = 2 they were being treated 1 and 2 years, respectively, with placebo or 10 mg prednisone daily.

Three of those 4 patients had very low GR-numbers at t=0: 3.3, 3.3, 3.6 and 8.4 fmol/10^6 cells, which rose to 8.0, 8.7, 11.2 and 10.4 fmol/10^6 cells, respectively after 1 year of treatment with 10 mg prednisone daily. Prednisone-responders, defined as the patients, who did not need SASP rescue medication at t=2 years (n=27; 13 females,14 males) did not have different GR-number at t=0 compared with prednisone-non-responders (n=8; 6 females, 2 males).

DISCUSSION

The GR-number of PBMC of early RA patients did not predict which patients were going to be prednisone responders clinically nor radiologically. However, 3 out of 4 prednisone users who developed osteoporotic vertebral fractures had a very low GR-number at t=0, which was strongly up-regulated at t=1 year. Whether this phenomenon is related to steroidosteoporosis needs further investigation. This cohort of early RA patients had a moderate disease activity, which did not change much during the follow up years. However progression of radiological joint damage was inhibited after 2 years of treatment .[8] Our results might have been different in very active early RA patients, who are reaching more complete remission with higher prednisone dosage. In addition the ratio of the isoforms of the GR, GRβ/GRα might be of importance in the patients ability to have a good response upon glucocorticoid therapy.[27,28]

The GR up-regulation was present in prednisone as well as placebo users and most prominent in women. In early female RA patients the GR-number at t = 0 is lower than the GR-number of age and sex matched healthy controls.[3] After two years the GR-number of the female patients with RA is up-regulated to the GR-number of healthy controls.[3] However, this up-regulation probably is not enough for the inflammatory situation of the RA patient. The increase of GR-number in PBMC in time was not due to leukocytosis as in our prednisone treated RA patients no leukocytosis was present after 1 and 2 years, neither a significant rise of lymphocytes or monocytes. The GR-number is not influenced by age or gender,[29] so the increase is not due to two years of aging of our patients either. Up-regulation of GR seems to reflect a compensatory mechanism of the HPA-axis as an answer upon an ongoing inflammatory process. This is suggested also by the finding that higher serum cortisol levels with disappearance of cortisol circadian rhythm is observed in RA patients with high activity.[30] Other studies in a variety of autoimmune

diseases show GR-down regulation upon glucocorticoid therapy.[31,32] However, this was most obvious at higher doses than the 10 mg prednisone daily used in our study. In addition, the fact that the HPA-axis seems impaired in early RA might play a role as well in clarifying that we did not find differences between 10 mg prednisone and placebo.[33] Monotherapy with 10 mg prednisone is disease modifying in respect to reduced progression of joint damage.[8] Combination with another DMARD gives an even better inhibition of radiological progression.[9-11] Since therapy with 10 mg prednisone gives the same up-regulation of the GR-number as therapy with placebo, monotherapy with 10 mg prednisone seems not able to fully suppress disease activity. This might be achieved by adding a DMARD or increasing the dose of prednisone. Increasing the dose of prednisone might result in responders and not-responders: in responders the GR-number might be less suppressed than in non-responders.

Concluding

This is the first study showing follow-up of GR-number of PBMC in early RA patients upon 10 mg prednisone daily or placebo. The GR up-regulation seems to reflect a recovery or compensatory mechanism as an answer upon an ongoing inflammatory process. This recovery might be not enough for the inflammatory situation at that moment, despite the fact that the progression of radiological damage is inhibited by 10 mg prednisone daily. The GR-number of PBMC of early RA patients did not predict which patients were going to be prednisone responders clinically nor radiologically.

REFERENCES

1. Schlaghecke R, Kornely E, Wollenhaupt J, Specker C. Glucocorticoid receptors in rheumatoid arthritis. Arthritis Rheum 1992; 35:740-744.
2. Schlaghecke R, Beuscher D, Kornely E, Specker C. Effects of glucocorticoids in rheumatoid arthritis. Diminished glucocorticoid receptors do not result in glucocorticoid resistance. Arthritis Rheum 1994; 37:1127-1131.
3. van Everdingen AA, Huisman AM, Wenting-Van Wijk MJ, Siewertsz van Reesema DR, Jacobs JW, Bijlsma JW. Down regulation of glucocorticoid receptors in early-diagnosed rheumatoid arthritis. Clin Exp Rheumatol 2002; In press.
4. Straub RH, Cutolo M. Involvement of the hypothalamic—pituitary—adrenal/gonadal axis and the peripheral nervous system in rheumatoid arthritis: viewpoint based on a systemic pathogenetic role. Arthritis Rheum 2001; 44:493-507.

5. Straub RH, Paimela L, Peltomaa R, Scholmerich J, Leirisalo-Repo M. Inadequately low serum levels of steroid hormones in relation to interleukin-6 and tumor necrosis factor in untreated patients with early rheumatoid arthritis and reactive arthritis. Arthritis Rheum 2002; 46:654-662.
6. Gudbjornsson B, Skogseid B, Oberg K, Wide L, Hallgren R. Intact adrenocorticotropic hormone secretion but impaired cortisol response in patients with active rheumatoid arthritis. Effect of glucocorticoids. J Rheumatol 1996; 23:596-602.
7. Masi AT, Chrousos GP. Hypothalamic-pituitary-adrenal-glucocorticoid axis function in rheumatoid arthritis. J Rheumatol 1996; 23:577-581.
8. van Everdingen AA, Jacobs JW, Siewertsz van Reesema DR, Bijlsma JW. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease modifying properties and side effects. A double-blind placebo-controlled clinical trial. Ann Intern Med 2002; 136:1-12.
9. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med 1995; 333:142-146.
10. Zeidler H, Rau R, Steinfeld P, et al. Efficacy and safety of low dose prednisolone in early rheumatoid arthritis. Arthritis Rheum 1999; 42:271
11. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997; 350:309-318.
12. Adcock IM, Nasuhara Y, Stevens DA, Barnes PJ. Ligand-induced differentiation of glucocorticoid receptor (GR) trans-repression and transactivation: preferential targetting of NF-kappaB and lack of I-kappaB involvement. Br J Pharmacol 1999; 127:1003-1011.
13. Da Silva JA, Bijlsma JW. Optimizing glucocorticoid therapy in rheumatoid arthritis. Rheum Dis Clin North Am 2000; 26:859-880.
14. Vanderbilt JN, Miesfeld R, Maler BA, Yamamoto KR. Intracellular receptor concentration limits glucocorticoid-dependent enhancer activity. Mol Endocrinol 1987; 1:68-74.
15. Buttgereit F, Da Silva JA, Boers M, Burmester GR, Cutolo M, Jacobs JW, et al. Standardised nomenclature for glucocorticoid doses and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. Ann Rheum Dis 2002; In press.

16. Tanaka H, Akama H, Ichikawa Y, Makino I, Homma M. Glucocorticoid receptor in patients with lupus nephritis: relationship between receptor levels in mononuclear leukocytes and effect of glucocorticoid therapy. J Rheumatol 1992; 19:878-883.
17. Sher ER, Leung DY, Surs W, Kam JC, Zieg G, Kamada AK, et al. Steroid-resistant asthma. Cellular mechanisms contributing to inadequate response to glucocorticoid therapy. J Clin Invest 1994; 93:33-39.
18. Fuchs HA, Pincus T. Reduced joint counts in controlled clinical trials in rheumatoid arthritis. Arthritis Rheum 1994; 37:470-475.
19. Boyum A. Isolation of mononuclear cells and granulocytes from human blood. Isolation of monuclear cells by one centrifugation, and of granulocytes by combining centrifugation and sedimentation at 1 g. Scand J Clin Lab Invest Suppl 1968; 97:77-89.
20. Costlow ME, Pui CH, Dahl GV. Glucocorticoid receptors in childhood acute lymphocytic leukemia. Cancer Res 1982; 42:4801-4806.
21. Steiner AE, Wittliff JL. A whole-cell assay for glucocorticoid binding sites in normal human lymphocytes. Clin Chem 1985; 31:1855-1860.
22. Wenting-Van Wijk MJ, Blankenstein MA, Lafeber FP, Bijlsma JW. Relation of plasma dexamethasone to clinical response. Clin Exp Rheumatol 1999; 17:305-312.
23. Papamichail M, Ioannidis C, Tsawdaroglou N, Sekeris CE. Translocation of glucocorticoid receptor from the cytoplasm into the nucleus of phytohemagglutinin-stimulated human lymphocytes in the absence of the hormone. Exp Cell Res 1981; 133:461-465.
24. Leach KL, Dahmer MK, Hammond ND, Sando JJ, Pratt WB. Molybdate inhibition of glucocorticoid receptor inactivation and transformation. J Biol Chem 1979; 254:11884-11890.
25. Scatchard G. The attraction of proteins for small molecules and ions. NY Acad Sci 1949; 51:660-672.
26. Lippman M, Barr R. Glucocorticoid receptors in purified subpopulations of human peripheral blood lymphocytes. J Immunol 1977; 118:1977-1981.
27. Derijk RH, Schaaf MJ, Turner G, Datson NA, Vreugdenhil E, Cidlowski J, et al. A human glucocorticoid receptor gene variant that increases the stability of the glucocorticoid receptor beta-isoform mRNA is associated with rheumatoid arthritis. J Rheumatol 2001; 28:2383-2388.
28. Bamberger CM, Bamberger AM, de Castro M, Chrousos GP. Glucocorticoid receptor beta, a potential endogenous inhibitor of glucocorticoid action in humans. J Clin Invest 1995; 95:2435-2441.

29. Tanaka H, Akama H, Ichikawa Y, Homma M, Oshima H. Glucocorticoid receptors in normal leukocytes: effects of age, gender, season, and plasma cortisol concentrations. Clin Chem 1991; 37:1715-1719.
30. Neeck G, Federlin K, Graef V, Rusch D, Schmidt KL. Adrenal secretion of cortisol in patients with rheumatoid arthritis. J Rheumatol 1990; 17:24-29.
31. Sanden S, Tripmacher R, Weltrich R, Rohde W, Hiepe F, Burmester GR, et al. Glucocorticoid dose dependent downregulation of glucocorticoid receptors in patients with rheumatic diseases. J Rheumatol 2000; 27:1265-1270.
32. Andreae J, Tripmacher R, Weltrich R, Rohde W, Keitzer R, Wahn U, et al. Effect of glucocorticoid therapy on glucocorticoid receptors in children with autoimmune diseases. Pediatr Res 2001; 49:130-135.
33. Dekkers JC, Geenen R, Godaert GL, van Doornen LJ, Bijlsma JW. Diurnal rhythm of salivary cortisol levels in patients with recent-onset rheumatoid arthritis. Arthritis Rheum 2000; 43:465-467.

Summary and Discussion

CHAPTER 7

SUMMARY

For 50 years, glucocorticoids (GC) are used for symptomatic treatment of rheumatoid arthritis (RA). In the last decade, results from clinical studies of treatment with GC as additional therapy to long-acting antirheumatic drugs in patients with early RA suggested also disease-modifying properties of GC in RA.

The aim of this thesis was to investigate disease-modifying properties and side effects of low-dose GC as monotherapy of patients with previously untreated early active RA in relation to clinical efficacy, general wellbeing and glucocorticoid receptors.

All 81 consecutive outpatients who participated in the clinical study had recently been diagnosed as having early active RA (disease duration less than a year) according to the ACR criteria, and were therapy naive (no disease-modifying-antirheumatic drugs [DMARDs] or GC). Age ranged from 24 to 82 years. The cohort consisted of 52 females and 29 males who attended the outpatient clinics of the Departments of Rheumatology of the Deventer and Zutphen Hospitals, the Netherlands. According to a computer-generated randomization at the Pharmacy, 41 patients were allocated to 10 mg prednisone orally daily and 40 to placebo. Non-steroidal anti-inflammatory drugs (NSAIDs) were allowed in both groups. After 6 months, sulphasalazine (2 gr. daily) could be prescribed as rescue medication in both groups. The study duration was 2 years, with an open follow-up third year. Ten patients dropped out of the study in the first 2 years for reasons not due to adverse or side effects of the study medication.

At baseline and every 3 months clinical parameters were assessed and every 6 months radiological studies were performed. The following variables were assessed: early morning stiffness, pain on a visual analogue scale (VAS), general well-being on a VAS, 28 joint scores for tenderness and swelling, grip strength, disability by a health assessment questionnaire (Dutch version of the HAQ), C-reactive protein (CRP) level and radiological scores of hands and feet (vd Heijde modification of the Sharp method). According to a standardized protocol, adverse and side effects were documented every 3 months.

In the first 3 months, patients on prednisone showed significant clinical improvement compared to those taking placebo. At 6 months this effect had disappeared except for the variables 28 joint score for tenderness and grip strength. However, the use

of additional therapies (NSAIDs, physiotherapy, paracetamol and local steroid injections) was significantly lower in the prednisone group. At 2 years, less than 35% of completers in both groups was on sulphasalazine rescue therapy.

From 12 months on, radiological scores showed significantly less progression of joint damage (erosions and joint space narrowing) in the prednisone group compared to the placebo group.

No clinically relevant adverse or side effects were observed, except for a higher incidence of new osteoporotic fractures in the prednisone group. These data are described and discussed in **Chapter 2**.

In **Chapter 3** we describe in more detail the results of the effect of low-dose GC on bone and the incidence of fractures. Except for 500 mg calcium supplement daily, no specific preventive measures were taken at the time the study started back in 1992. After 2 years prednisone was tapered down and stopped. The effect on bone was assessed in the first two years and also in the third year. At the start of the study and every 6 months, X-rays of the twelfth thoracic and all lumbar vertebrae were scored using the Kleerekoper method, and every year biochemical parameters of bone metabolism and bone mineral density (BMD) were assessed.

At the start of the study there was one patient in each group with one vertebral fracture. During the study there was a higher incidence of lumbar vertebral fractures in the prednisone group than in the placebo group: 7 vs 4 respectively. One patient in the prednisone group suffered an osteoporotic fracture of the pelvis. In the 2-year study and the subsequent follow-up year, no other peripheral fractures were seen in either group. No significant changes from baseline in BMD of the hips and lumbar spine were seen in either group. The same pattern was observed in the third year. There was no correlation between changes in serum osteocalcin and BMD.

Low-dose prednisone for patients with early active RA seems to increase the risk of fractures, despite the observed lack of change in BMD. This confirms the hypothesis that GC treatment may lead to fractures also via other effects on bone than decrease of bone mineral density, i.e. via changes in bone strength and structure.

In our analysis a discrepancy was found between the significantly sustained retardation of joint damage and only transient reduction of disease activity in the prednisone group and no enduring differences in disease activity variables between the prednisone group and the placebo group. We investigated whether this discrepancy also extended to parameters of general wellbeing: the VDF (Dutch version of the HAQ), the IRGL (Dutch version of the AIMS), the VAS morning

pain and the VAS general wellbeing. We indeed found almost no differences in parameters of general wellbeing in both groups. The lack of differences between the two groups regarding not only variables of disease activity but also variables of wellbeing is most probably due to a 2-fold increase in the (free) use of additional therapies (NSAIDs, analgesics, physiotherapy and local steroid injections only if strictly necessary) in the placebo group compared to the prednisone group. These results are described in **Chapter 4**.

In patients with RA of longer duration, glucocorticoid receptor (GR) down-regulation has been reported without change in cortisol levels. If this down-regulation would also be present in patients with early RA, it could play a role in the aetiopathogenesis of RA. In the patients of our study, and age and sex matched healthy controls, blood samples were taken between 8-10 AM. GR-expression (GR-number and GR-affinity), serum cortisol levels, erythrocyte sedimentation rate (ESR), CRP, painful and swollen joints were measured. A significantly lower GR-number was found in female patients compared with sex and age matched healthy controls, but not in male patients. Neither in female nor in male patients, correlations were found between GR-expression and parameters of disease activity nor was there a relation between GR-expression and serum cortisol levels. So in our study, changes in GR-expression or serum cortisol were not a general phenomenon, being only present in females and they were not related to disease activity. From these results it seems unlikely that GR-expression per se plays a major role in the aetiopathogenesis of RA. This part of the study is described in **Chapter 5**.

Because we studied a cohort of patients with DMARD and GC naive early active RA it was of interest to search for some predictive values for the effect of GC on the disease. It is common knowledge that not all RA patients respond in the same way to GC treatment; some do not respond at all, others do at low doses, while others require larger doses for seemingly identical clinical situations. Therefore, we investigated the individual response to GC treatment after 1 and 2 years: do responders differ from non-responders in disease activity and outcome measures? From the patients of the study blood samples were taken between 8-10 AM. GR-expression was measured from start and every 12 months and for each individual compared to parameters of disease activity, general wellbeing and joint damage. Also, the effects of GC on the proliferative response of peripheral blood mononuclear cells (PBMC) in those patients were assessed every year. We found in our study an increase (up-regulation) of the GR-number in time both in females

and in males, in the prednisone group as well as in the placebo group. This was most obvious in females. However, no correlations were found between the GR-number and the radiological scores in the prednisone users after 2 years neither with treatment nor with BMD. Prednisone-responders, defined as the patients who did not use or had not used SASP rescue medication after 2 years, did not have a different GR-number compared with prednisone-non-responders. So, prediction with GR-number of the effect of GC was not possible. This is described in **Chapter 6**.

DISCUSSION

We were able to study benefits and risks of a 2-year treatment with 10 mg prednisone daily compared to placebo, independent of other therapies, among patients with early active DMARD-naive RA. This unique clinical setting is unlikely to recur. The study was designed in 1991 and patients were included from 1992 to 1995. Nowadays such design in RA, testing an active drug against placebo, would be considered unethical because we now know joint damage is an early feature of the disease.[1] Therefore, early and aggressive therapy is currently advocated.[2-4]

We showed significant retardation of joint damage in patients with early RA treated with 10 mg prednisone daily. There was a sustained reduction in the rate of joint damage in the second year compared to placebo. Zeidler et al. also saw this effect in the study with 5 mg prednisolone daily in combination with either gold sodium thiomalate or methotrexate.[5] In the cohort of RA patients of Kirwan and Hickling, et al. radiologically detected joint damage resumed after discontinuation of 7.5 mg prednisolone daily in combination with a variety of DMARDs after 2 years.[6, 7] In the cohort of RA patients of Boers and Landewé treated with a step-down combination therapy starting with 60 mg prednisolone there was a sustained reduction of the rate of radiological progression of joint damage up till 4-5 years.[8, 9] They suggested a 'window of opportunity' in the first 2 years of the disease in which aggressive therapy limits joint destruction over time.

As was expected, patients in the prednisone group experienced significant reduction in parameters of disease activity in the first 3 months of the study. Remarkably however, the clinical benefit in this group disappeared between 3 and 6 months after which there was no difference anymore between the prednisone and the placebo group, but the use of additional therapies in the prednisone group was about 50% of that of the placebo group. The increased use of additional therapies in the placebo group probably counterbalances the beneficial effect of prednisone in the

prednisone group. After 6 months, sulphasalazine (2 gr daily) could be prescribed as rescue medication in both groups. Although radiographs of hands and feet were performed every 6 months, reading took place at the end of the study according to the protocol (1998). So, without knowledge of possible joint damage and thus only on clinical grounds, less than 35% of patients at the end of the 2-year study, equally divided over both groups, was on sulphasalazine. The low prescription rate for sulphasalazine therapy was apparently influenced by reduced disease symptoms, due to the free use of additional therapies such as analgesics and NSAIDs, but the radiologically detected joint damage would in normal daily clinical practice have warranted earlier intervention.

Results from several recent studies indicate clinical benefit of longer duration than 3-6 months, although still transient, when combination therapy of DMARDs (such as sulphasalazine, gold salts and methotrexate) and prednisone was applied.[6, 8, 10] So, for various reasons, prednisone therapy should be added to DMARD therapy in daily clinical practice.

In our analysis, also in contrast with the significant benefit of prednisone on radiological joint damage, there were no statistically significant differences in parameters for wellbeing between both groups during the study. In our view, the increased use of additional therapies (NSAIDs, analgesics, local steroid injections and physiotherapy) in the placebo group masked the beneficial effect of prednisone not only on clinical parameters but also on wellbeing. Up till now, in studies of patients with RA comparing different treatment strategies the effects of additional therapies are not evaluated. In future clinical trials, in our view the use of additional therapies should thus be taken into account and reported upon analysing differences in effect between two drug therapies.

To put it the other way around, prednisone had a sparing effect on the use of NSAIDs and other additional therapies. This could explain why in the prednisone group peptic ulceration occurred less frequently (one patient) than in the placebo group (two patients): the increased risk of peptic ulceration by the combination of NSAID and prednisone was counterbalanced by the use of less NSAIDs in the prednisone group. So, the risk of gastric peptic ulceration when adding prednisone to the therapy in daily practice could be less than anticipated by the NSAID sparing effect of prednisone.

In the prednisone group more osteoporotic fractures occurred compared to the placebo group; the difference however did not reach statistical significance probably

because of small numbers. In contrast, no significant changes from baseline in BMD of hips and lumbar spine were seen in either group. The same pattern was observed in the third year. Apparently, changes in bone strength and structure, in addition to changes in BMD, may lead to fractures in patients with RA treated with GC, which confirms earlier reports.[11] Due to the observed lack of correlation between GC-induced osteoporotic fractures and BMD, other techniques assessing bone strength and structure like quantitative ultrasound should be considered. A methodological problem of quantitative ultrasound assessment however is that it cannot be used as follow-up measurements. In contrast to the negative effects on bone, low-dose GC treatment of patients with RA reduces disease activity and enhances mobility, effects that are in itself anti-osteoporotic.

The common strategy at the time our study started to prevent secondary osteoporosis was a daily supplement of 500 mg calcium only. Nowadays prevention with bisphosphonates in combination with supplementary calcium and vitamin D is considered the potent anti-osteoporosis strategy of choice in the treatment with GC.

In patients with RA of longer duration, glucocorticoid receptor (GR) down-regulation has been reported without change in cortisol levels. This could play a role in the etiopathogenesis of RA. Changes in GR-expression as well as serum cortisol were not a general phenomenon in our early diagnosed RA patients however, being only present in females but not in males and these changes were not related to disease activity. So, in our view, it seems unlikely that GR-expression plays a major role in the etiopathogenesis of RA, but it might be a co-factor determining the difference in incidence of RA, being less prevalent in males than in females.

The GR-number of peripheral blood mononuclear cells (PBMC) of early RA patients did not predict which patients were going to be prednisone responders, clinically nor radiologically. GR up-regulation in the first two years of the RA patient, regardless of the treatment might reflect a compensatory mechanism of the increasing HPA-axis insufficiency due to the ongoing inflammatory process. However, this up-regulation might not be enough to efficiently control the inflammatory situation.

Assessment of the ratio of the isoforms of GR, GR ß/GR a, might be a better method to predict the patients ability to have a good response upon GC therapy. [12] To investigate the role of GR in the etiopathogenesis of RA and in the prediction of prednisone responders in future clinical trials assessment of the ratio of the isoforms of GR is warranted.

Monotherapy with a 10 mg prednisone regimen in patients with early active DMARD-naive RA has potent disease modifying properties. So, especially since potential serious adverse effects are more easily managed today, GC could not only be used temporarily for complications and exacerbations of RA, to bridge the lag-time for remission induction of recently started DMARDs and as local injections, but also as a long-term DMARD regimen in early RA in combination with other DMARDs.[13, 14]

At the time of the study 10 mg prednisone was considered to be low-dose, although in daily clinical practice there is now a tendency to regard 7.5 mg prednisone or even less as low-dose. Due to new insights in mechanism of action of GC, clinical experience and the results of a meta-analysis of toxicity of GC in patients with RA, a low-dose regimen is nowadays defined as low as 7.5 mg or less.[1, 15, 16] The questions arise if a low-dose prednisone regimen also has joint protective properties in patients with RA of longer duration and if there is a place for low-dose prednisone when patients with RA are treated with aggressive DMARDs strategies (such as methotrexate up to 30 mg weekly) and/or biologicals.

Future studies should thus concentrate first on the question whether 10 mg prednisone also is beneficial on joint damage if patients are intensively treated with DMARDs and if the answer is positive, on the search for the lowest dosis of GC in combination with aggressive DMARD therapy, in order to fully suppress progression of radiological damage as well as inflammation.

REFERENCES

1. Pincus T, Sokka T, Stein CM. Are long-term very low doses of prednisone for patients with rheumatoid arthritis as helpful as high doses are harmful? Ann Intern Med 2002;136:76-8.
2. Heide A, Jacobs JWG, Bijlsma JWJ, et al. The effectiviness of early management with "second-line" antirheumatic drugs: a randomised controlled trial. Ann Intern Med 1996;124:699-707.
3. Kirwan JR. Conceptual issues in scoring radiographic progression in rheumatoid arthritis. J Rheumatol 1999;26:720-5.
4. Tugwell P, Boers M. Long acting drug combinations in rheumatoid arthritis, updated overview. In: Wolfe F, Pincus T (Eds). Rheumatoid arthritis: pathogenesis, assessment, outcome and treatment. New York: Marcel Dekker 1994;357-71.
5. Wassenberg S, Rau R, Zeidler H. Low dose prednisolone therapy (LDPT) retards radiographically detectable destruction in early rheumatoid arthritis. Arthritis Rheum 1999;42(Suppl):S243 (Abstract).

6. Kirwan JR. Arthritis and Rheumatism Council Low-dose Glucocorticoid study Group: The effect of glucocorticoid on joint destruction in RA. N Engl J Med 1995;333: 142-6.
7. Hickling P, Jacoby RK, Kirwan JR and the Arthritis and Rheumatism Council Low Dose Glucocorticoid Study Group. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. Br J Rheumatol 1998;37:930-6.
8. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309-18.
9. Landewé RBM, Boers M, Verhoeven AC, et al. COBRA Combination therapy in patients with early rheumatoid arthritis. Long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46:347-56.
10. Zeidler H, Rau R, Steinfeld P. Efficacy and safety of low dose prednisolone in early rheumatoid arthritis. Arthritis Rheum 1999;42(Suppl):S271 (Abstract).
11. Buckley LM. Clinical and diagnostic features of glucocorticoid-induced osteoporosis. Clin Exp Rheumatol 2000;18:41-3.
12. Bijlsma JWJ, Straub RH, Masi T, et al. Neuroendocrine immune mechanisms in rheumatic diseases. Trends Immunol 2002;2:59-61.
13. Weusten BLAM, Jacobs JWG, Bijlsma JWJ. Corticosteroid pulse therapy in active rheumatoid arthritis. Semin Arthritis Rheum 1993;23:183-92.
14. Jacobs JWG, Geenen R, Evers AWM, et al. Short term effects of corticosteroid pulse treatment on disease activity and the wellbeing of patients with active rheumatoid arthritis. Ann Rheum Dis 2001;60:61-4.
15. Saag KG, Criswell LA, Sems KM, et al. Low-dose corticosteroids in rheumatoid arthritis: A meta-analysis of their moderate-term effectiveness. Arthritis Rheum 1996;39:18-25.
16. Buttgereit F, Silva JAP da, Boers M, et al. Standardised nomenclature for glucocorticoid doses and glucocorticoid treatment regimens: current questions and temptative answers in rheumatology. Ann Rheum Dis 2002, in press.

Samenvatting en Discussie

SAMENVATTING

Reeds meer dan 50 jaar worden glucocorticoïden (GC) toegepast als symptomatische behandeling van patiënten met reumatoïde artritis (RA). In het laatste decennium maken resultaten van klinische trials van behandeling met GC als toegevoegde therapie bij langwerkende antireumatica bij patiënten in een vroeg stadium van RA het aannemelijk dat GC naast symptoomverlichting ook ziektebeïnvloedende eigenschappen bij RA hebben.

Het doel van dit proefschrift is om ziektebeïnvloedende eigenschappen en bijwerkingen van laaggedoseerde GC als monotherapie bij patiënten met niet eerder behandelde vroege RA te onderzoeken en te beschrijven in relatie tot klinische effectiviteit, algemeen welbevinden en GC receptoren.

Bij alle 81 opeenvolgende poliklinische patiënten welke deelnamen aan het onderzoek was recent vroege actieve RA vastgesteld (ziekteduur minder dan een jaar) volgens de criteria van het American College of Rheumatology (ACR) en zij waren niet eerder behandeld met langwerkende ziektebeïnvloedende geneesmiddelen [disease-modifying antirheumatic drugs (DMARDs)] of GC. De leeftijd varieerde van 24 t/m 82 jaar. De patiëntengroep bestond uit 52 vrouwen en 29 mannen die de poliklinieken bezochten van de afdeling Reumatologie van de ziekenhuizen in Deventer en Zutphen. Volgens een door een computer gegenereerde randomisatie in de Apotheek Deventer Ziekenhuis kregen 41 patiënten dagelijks 10 mg prednison in tabletvorm toegewezen en 40 patiënten kregen placebo tabletten. In beide groepen was het gebruik van niet-steroïde pijnstillende en ontstekingswerende middelen toegestaan [non-steroidal anti-inflammatory drugs (NSAIDs)]. Als ontsnappings-clausule kon in beide groepen sulfasalazine (2 gram dagelijks) aan de behandeling worden toegevoegd als de ernst van de klinische verschijnselen van de RA dat noodzakelijk maakte. De duur van de trial bedroeg 2 jaar met een open nacontrole van 1 jaar. Tien patiënten verlieten voortijdig het onderzoek in de eerste 2 jaar om redenen die niet samenhingen met bijwerkingen van de trialmedicatie.

In de uitgangssituatie en daarna iedere 3 maanden werden klinische parameters gemeten en iedere 6 maanden werden röntgenfoto's van handen en voorvoeten gemaakt. De volgende variabelen werden gemeten: duur van stijfheid vroeg in de ochtend, pijn uitgedrukt op een visuele analoge schaal [visual analogue scale (VAS)], algemeen welbevinden op een VAS, 28 gewrichtsscore voor pijn bij druk en die voor zwelling, knijpkracht, functionele beperking middels een vragenlijst dagelijks functioneren [VDF, een voor Nederland gevalideerde versie van de Health Assessment Questionnaire (HAQ)], C-reactief proteïne in serum (CRP) en

radiologische scores van handen en voorvoeten (volgens de vd Heijde modificatie van de Sharp methode). Volgens een gestandaardiseerd protocol werden bijwerkingen elke 3 maanden gedocumenteerd.

In de eerste 3 maanden was er een statistisch significante klinische verbetering waarneembaar bij de met prednison behandelde patiënten ten opzichte van de met placebo behandelden. Na 6 maanden was dit effect verdwenen met uitzondering van de 28 gewrichtsscore voor pijn en de knijpkracht. Het gebruik van bijkomende therapieën (NSAIDs, fysiotherapie, paracetamol en locale steroïdinjecties) was echter significant lager in de prednison groep. Na 2 jaar gebruikte minder dan 35% van de patiënten die de trial voltooiden in beide groepen sulfasalazine als ontsnappings-medicatie.

Vanaf 12 maanden toonden de röntgenfoto's statisch significant minder progressie van gewrichtsschade (erosies en gewrichtsspleetversmalling) in de prednison groep vergeleken met de placebo groep.

Er werden geen klinisch relevante bijwerkingen waargenomen behalve een hogere incidentie van nieuwe osteoporotische fracturen in de prednison groep. Deze gegevens worden beschreven en bediscussieerd in **Hoofdstuk 2**.

In **Hoofdstuk 3** beschrijven wij meer gedetailleerd de bevindingen omtrent het effect van laaggedoseerde GC op het bot en de incidentie van fracturen. Met uitzondering van 500 mg calcium supplement dagelijks werden geen specifieke preventieve maatregelen tegen het optreden van osteoporose getroffen ten tijde van de start van het onderzoek in 1992. Na 2 jaar werd de prednison afgebouwd en gestaakt. Het effect op het bot werd zowel in de eerste 2 jaar als in het derde jaar gemeten. Bij de start van de trial en vervolgens iedere 6 maanden werden röntgenfoto's vervaardigd van de 12^{e} thoracale en alle lumbale wervels welke na 2 jaar werden beoordeeld volgens de Kleerekoper methode; tevens werden jaarlijks biochemische parameters van de botstofwisseling gemeten en werd een botdichtheidsmeting [bone mineral density (BMD)] verricht.

Bij aanvang van het onderzoek was er in iedere groep één patiënt met één wervelfractuur. Tijdens de trial was er een hogere incidentie van lumbale wervelfracturen in de prednison groep dan in de placebo groep: 7 vs 4 respectievelijk. Eén patiënt in de prednison groep kreeg een osteoporotische bekkenfractuur. In de 2-jaarstrial en in het vervolgjaar ontstonden geen andere perifere fracturen in beide groepen. BMD metingen van heupen en lumbale wervelkolom veranderden niet significant ten opzichte van de uitgangssituatie in beide groepen. Hetzelfde patroon

werd in het 3e jaar waargenomen. Er was geen correlatie tussen veranderingen in osteocalcine in het serum en BMD.

Laaggedoseerde prednisonbehandeling bij patiënten met vroege actieve RA lijkt het risico van fracturen te verhogen, ondanks het in ons onderzoek waargenomen ontbreken van een statistisch significante verandering in BMD. Dit bevestigt de hypothese dat behandeling met GC tot fracturen kan leiden ook via andere effecten op het bot dan verlaging van de botdichtheid, d.w.z. via veranderingen in botsterkte en –structuur.

In onze analyse werd een discrepantie gevonden tussen de significante aanhoudende vertraging van gewrichtsschade enerzijds en slechts voorbijgaande vermindering van ziekteactiviteit in de prednison groep en geen blijvende verschillen in variabelen van ziekteactiviteit tussen de prednison groep en de placebo groep anderzijds. Wij onderzochten of deze discrepantie ook gevonden kon worden in beide groepen in parameters voor algemeen welbevinden: de VDF, de IRGL (invloed van reuma op gezondheid en leefwijze, een voor Nederland gevalideerde zelfbeoordelingslijst); de VAS ochtendpijn en de VAS algemeen welbevinden. Wij vonden inderdaad vrijwel geen verschillen in parameters voor algemeen welbevinden tussen beide groepen. Het ontbreken van verschillen tussen de twee groepen voor wat betreft zowel de variabelen van ziekteactiviteit alsook die voor algemeen welbevinden is zeer waarschijnlijk toe te schrijven aan verdubbeling van het (vrije) gebruik van bijkomende therapieën (NSAIDs, analgetica, fysiotherapie en locale steroid injecties alleen wanneer strikt noodzakelijk) in de placebo groep vergeleken met de prednison groep. Deze resultaten worden beschreven in **Hoofdstuk 4**.

Bij patiënten met langer bestaande RA wordt vermindering van het aantal glucocorticoïd receptoren (GR) in de literatuur gemeld zonder verandering in serum cortisolspiegels. Als deze vermindering ook aanwezig zou zijn bij patiënten met vroege RA, dan zou down-regulatie van GR een rol kunnen spelen in de etiopathogenese van RA. Bij de patiënten in ons onderzoek en bij voor leeftijd en geslacht gepaarde gezonde controles werden bloedmonsters afgenomen tussen 8 en 10 uur ‘s ochtends. GR-expressie (GR-aantal en GR-affiniteit), serum cortisolspiegels, bloedbezinkingssnelheid van erytrocyten (BSE), CRP en het aantal pijnlijke en gezwollen gewrichten werden onderzocht. Er werd een significant lager aantal GR gevonden bij vrouwelijke patiënten in vergelijking met geslacht en leeftijd gepaarde controles, echter niet bij mannelijke patiënten. Bij vrouwelijke noch mannelijke patiënten werden correlaties gevonden tussen GR-expressie en parameters

van ziekteactiviteit, noch was er relatie tussen GR-expressie en serum cortisolspiegels. Veranderingen in GR-expressie of serum cortisolspiegels waren in ons onderzoek slechts aanwezig bij vrouwen, was dus geen algemene bevinding en bovendien was er geen relatie met ziekteactiviteit. Gezien deze bevindingen lijkt het onwaarschijnlijk dat GR-expressie op zich een belangrijke rol speelt bij het ontstaan van RA. Dit gedeelte van de trial wordt beschreven in **Hoofdstuk 5**.

Aangezien wij patiënten met vroege actieve RA bestudeerden die DMARD en GC naïef waren, was het interessant om naar een mogelijke voorspellende waarde te zoeken voor het effect van GC op de ziekte. Het is algemeen bekend dat niet alle RA patiënten op dezelfde wijze reageren op behandeling met GC; sommigen reageren helemaal niet, anderen doen dat al op lage doses terwijl weer anderen juist hogere doseringen nodig hebben in ogenschijnlijk vergelijkbare klinische situaties. Daarom bestudeerden wij de individuele respons op behandeling met GC na 1 en 2 jaar: verschillen responders van non-responders in GC aantal? Bij patiënten in de trial werden bloedmonsters afgenomen tussen 8 en 10 uur 's ochtends. GR-expressie werd gemeten bij de start en verder jaarlijks en voor ieder individu vergeleken met parameters van ziekteactiviteit, algemeen welbevinden en gewrichtsschade. Daarnaast werden de effecten van GC op de proliferatieve respons van mononucleaire cellen van het perifere bloed [peripheral blood mononuclear cells (PBMC)] van deze patiënten ieder jaar onderzocht. Wij vonden in ons onderzoek toename (up-regulatie) van het aantal GR in de tijd zowel bij vrouwen als bij mannen en zowel in de prednison- als in de placebo groep. Dit effect is het meest duidelijk bij vrouwen. Daarentegen werden tussen het aantal GR en de radiologische scores bij de prednison gebruikers na 2 jaar geen correlaties gevonden noch tussen aantal GR en de aard van de behandeling, of de BMD. Prednison-responders, gedefinieerd als de patiënten die geen sulfasalazine als ontsnappingstherapie hoefden te gebruiken tijdens de 2-jarige trial of als de patiënten die geen sulfasalazine gebruikten na 2 jaar, verschilden niet wat betreft GR aantal vergeleken met prednison non-responders. Met andere woorden, voorspelling ten aanzien van het effect van GC aan de hand van het aantal GR was niet mogelijk. Deze bevindingen worden besproken in **Hoofdstuk 6**.

DISCUSSIE

Wij konden de voor- en nadelen van een behandeling met 10 mg prednison daags gedurende 2 jaar vergelijken met placebo, onafhankelijk van DMARDs bij patiënten met een vroege actieve DMARD-naïeve RA. Het is onwaarschijnlijk dat deze unieke

klinische setting kan worden herhaald. De trial was opgezet in 1991 en patiënten werden geïncludeerd van 1992 tot 1995. Tegenwoordig zou een dergelijk onderzoek met testen van een bewezen effectief geneesmiddel tegen placebo als onethisch worden beschouwd, aangezien wij nu weten dat gewrichtsschade een vroeg kenmerk is van de ziekte. Daarom wordt vroege en agressieve behandeling tegenwoordig aanbevolen.

Wij toonden significante vertraging van gewrichtsschade aan bij patiënten met vroege RA behandeld met 10 mg prednison dagelijks. De vermindering van de progressie van de gewrichtsschade hield aan in het 2e jaar in vergelijking met placebo. Zeidler et al. zagen dit effect eveneens in hun trial met 5 mg prednisolon in combinatie met het goudzout aurothiomalaat of met methotrexaat. In de groep RA patiënten van Kirwan en Hickling et al. nam de radiologisch vastgestelde gewrichtsschade weer toe na staken van 7,5 mg prednisolon dagelijks in combinatie met verscheidene DMARDs na 2 jaar. In de groep RA patiënten van Boers en Landewé behandeld met een stapsgewijs afbouwschema met combinatietherapie startend met 60 mg prednisolon werd aanhoudende vermindering van radiologische progressie van gewrichtsschade waargenomen gedurende 4 à 5 jaar. Zij stelden dat er een 'window of opportunity' is in de eerste 2 jaar van de ziekte, waarin agressieve therapie gewrichtsschade voor langere tijd kan beperken.

Zoals verwacht was er bij onze patiënten in de prednison groep significante vermindering van ziekteactiviteit in de eerste 3 maanden van het onderzoek. Opvallend echter verdween de klinische verbetering in deze groep tussen 3 en 6 maanden vergeleken met de placebo groep. Maar het gebruik van aanvullende behandelingen was in de prednison groep ongeveer de helft van dat in de placebo groep. Het effect van het hogere gebruik van bijkomende therapieën in de placebo groep weegt waarschijnlijk op tegen het gunstige klinisch effect van prednison in de prednison groep. Alleen als het klinisch strikt noodzakelijk was kon na 6 maanden sulfasalazine (2 gram dagelijks) worden voorgeschreven als ontsnappingsmedicatie in beide groepen. Ofschoon iedere 6 maanden röntgenfoto's van handen en voorvoeten werden gemaakt, vond beoordeling pas plaats aan het eind van de trial volgens het onderzoeksprotocol (1998). Daarom was, zonder de wetenschap van eventuele radiologische gewrichtsschade en progressie daarvan en dus uitsluitend op klinische gronden, minder dan 35% van de patiënten aan het eind van de 2-jaars trial, evenredig verdeeld over beide groepen, behandeld met sulfasalazine. Het lage voorschrijf-percentage voor sulfasalazine behandeling was kennelijk beïnvloed door

gereduceerde ziekteverschijnselen ten gevolge van het vrije gebruik van aanvullende therapieën waaronder pijnstillers, NSAIDs, fysiotherapie en locale injecties. In de normale dagelijkse praktijk had de radiologisch vastgestelde gewrichtsschade ongetwijfeld tot eerdere interventie met DMARDs aanleiding gegeven.

Resultaten van enkele recent uitgevoerde onderzoeken wijzen op klinische verbetering van langere duur dan 3-6 maanden, als een combinatiebehandeling van DMARDs (zoals sulfasalazine, goudzouten en methotrexaat) en prednison wordt toegepast. Daarom dienen DMARDs te worden toegevoegd aan behandeling met prednison in de dagelijkse klinische praktijk.

Uit onze analyse werden, eveneens in tegenstelling tot het significante gunstige effect van prednison op gewrichtsschade, geen statistisch significante verschillen waargenomen in parameters voor algemeen welbevinden tussen de beide groepen gedurende het onderzoek. Naar ons inzicht maskeerde het toegenomen gebruik van aanvullende therapieën (NSAIDs, pijnstillers, lokale steroïd injecties en fysiotherapie) in de placebo groep het gunstige effect van prednison, niet alleen op klinische parameters maar ook op die van het algemeen welbevinden. Tot nu toe worden de effecten van aanvullende therapieën in trials met RA patiënten waarin verschillende behandelstrategieën worden vergeleken niet geëvalueerd. In toekomstige klinische trials dient naar onze mening met het gebruik van aanvullende behandelingen rekening te worden gehouden en dient dit gebruik te worden gerapporteerd bij de analyses van verschillen van effect tussen twee geneesmiddelen.

Men kan ook stellen dat prednison een sparend effect op het gebruik van NSAIDs en andere aanvullende behandelingen had. Dit zou kunnen verklaren waarom in de prednison groep er minder vaak (1 patiënt) klinisch relevante peptische ulceratie optrad dan in de placebo groep (2 patiënten): het verhoogde risico op peptische ulceratie door de combinatie van NSAID en prednison werd tenietgedaan door het lagere gebruik van NSAIDs in de prednison groep. Met andere woorden, het risico van peptische ulceratie wanneer prednison aan de behandeling wordt toegevoegd kan in de dagelijkse praktijk wel eens lager uitvallen dan verwacht door het NSAID sparende effect van prednison.

In de prednison groep traden meer osteoporotische fracturen op vergeleken met de placebo groep; het verschil bereikte echter geen statische significantie, waarschijnlijk vanwege de kleine aantallen. Daarentegen werden in beide groepen geen significante veranderingen waargenomen in de BMD van heupen en lumbale wervelkolom. Hetzelfde patroon werd gezien in het 3^{e} jaar. Kennelijk kunnen veranderingen in botsterkte- en structuur, naast veranderingen in de BMD, leiden

tot fracturen bij RA patiënten behandeld met GC, hetgeen eerdere rapporten bevestigt. Vanwege het waargenomen gebrek aan correlatie tussen GC-geïnduceerde osteoporotische fracturen en BMD zouden technieken om botsterkte- en structuur te meten moeten worden overwogen zoals kwantitatieve echografie. Deze techniek kan echter niet gebruikt worden in follow-up metingen aangezien het ontbreken van standaardisering een methodologisch probleem is. In tegenstelling tot de negatieve effecten op het bot vermindert laaggedoseerde GC behandeling bij RA patiënten de ziekteactiviteit en verhoogt deze therapie de mobiliteit, effecten die osteoporose tegengaan.

De gebruikelijke strategie ten tijde van de start van ons onderzoek ter voorkoming van secundaire osteoporose bestond slechts uit een dagelijks supplement van 500 mg calcium. Tegenwoordig worden bisfosfonaten in combinatie met aanvullend calcium en vitamine D beschouwd als krachtige anti-osteoporose strategie van keuze bij de behandeling met GC.

Bij patiënten met langer bestaande RA wordt vermindering van het aantal GR gerapporteerd zonder verandering in serum cortisolspiegels. Dit zou een rol kunnen spelen in de etiopathogenese van RA. Veranderingen in GR-expressie alsook in serum cortisolspiegels waren echter geen algemeen verschijnsel bij onze patiënten met vroege RA. Veranderingen werden alleen bij vrouwen waargenomen en niet bij mannen en verder toonden deze veranderingen geen relatie met ziekteactiviteit. Dus lijkt het naar onze mening onwaarschijnlijk dat GR-expressie een belangrijke rol speelt bij de etiopathogenese van RA, maar het zou een co-factor kunnen zijn die de incidentie van RA beïnvloedt daar RA minder vaak voorkomt bij mannen dan bij vrouwen.

Het aantal GR van PBMC bij patiënten met vroege RA voorspelde niet welke patiënten prednison-responders zouden worden, klinisch noch radiologisch. GR toename (up-regulatie) in de eerste 2 jaar bij RA patiënten, onafhankelijk van de behandeling, zou een compensatoir mechanisme van de toenemende hypothalamus-hypofyse-bijnieras (HHB-as)-insufficiëntie kunnen zijn bij een voortgaand ontstekingsproces. Deze up-regulatie is echter niet voldoende om het ontstekingsproces efficiënt te onderdrukken.

Bepaling van de ratio van isovormen van GR, GRβ/GRα, zou een betere methode kunnen zijn om de kans van een patient te voorspellen op een goede respons op GC behandeling. Om de rol van GR te bestuderen in de etiopathogenese van RA en in de voorspelling van prednison-responders is het bepalen van de ratio van de GR isovormen in toekomstige klinische onderzoeken wenselijk.

Monotherapie met een schema van 10 mg prednison bij patiënten met een vroege actieve DMARD-naïeve RA heeft krachtige ziektebeïnvloedende eigenschappen. Dus, mede aangezien potentiële ernstige bijwerkingen tegenwoordig beter voorkomen kunnen worden, zouden GC niet alleen tijdelijk gebruikt kunnen worden bij complicaties en exacerbaties van RA en om de tijd te overbruggen voor remissie-inductie van recent gestarte DMARDs optreedt of als locale injecties, maar ook als langwerkend DMARD regime bij vroege RA in combinatie met andere DMARDs.

Ten tijde van de trial werd 10 mg prednison beschouwd als een lage dosis. Dankzij nieuwe inzichten in het werkingsmechanisme van GC, klinische ervaringen en de resultaten van een meta-analyse omtrent toxiciteit van GC bij patiënten met RA wordt een laaggedoseerd regime tegenwoordig gedefinieerd als 7,5 mg of minder.

De vraag rijst of een lagere dosis prednison eveneens gewrichtsbeschermende eigenschappen heeft bij patiënten met langer bestaande RA en of er een plaats is voor laaggedoseerde prednison behandeling wanneer patiënten met RA worden behandeld met agressieve DMARD-strategieën (zoals methotrexaat tot 30 mg per week) en/of biologische middelen (zoals anti-TNF-α en anti-IL-1receptor antagonisten).

Toekomstige onderzoeken zouden zich eerst moeten concentreren op de vraag of 10 mg prednison ook een gunstig effect heeft op gewrichtsschade indien patiënten intensief worden behandeld met DMARDs en als het antwoord positief is, op het zoeken naar de laagste effectieve dosis GC in combinatie met agressieve DMARD behandeling teneinde progressie van radiologische gewrichtsschade alsook het ontstekingsproces zo volledig mogelijk te onderdrukken.

Dankwoord

Velen zijn behulpzaam geweest bij het tot stand komen van dit proefschrift. Allen wil ik hierbij bedanken en beperk mij tot het noemen van hen die rechtstreeks hierbij betrokken zijn geweest.

Allereerst alle trouwe reumapatiënten die deelnamen aan het onderzoek en jaarlijks naar Utrecht reisden; twee van hen beleefden hun mooiste dag uut hun léèven toen zij bij windkracht 10 op het Centraal Station Utrecht strandden met honderden andere reizigers en genoten van spontane muziek en soep van het Leger des Heils. Sommigen waren nog nooit eerder de IJssel over geweest.

In het bijzonder wil ik danken Hans Bijlsma (promotor): voor je visie om mij als moeder met jonge kinderen een promotieonderzoek toe te dichten in je onderzoekslijn. Met bewondering heb ik jou een relatief kleine universitaire afdeling zien opbouwen tot een hoogwaardige kliniek en wetenschappelijk centrum. Jij hebt in deze lange periode mij steeds gesteund en de rode draad vastgehouden waarin ik, zonder jou, als een kluwen was geëindigd. Je moet je vermand hebben zo lang in mij te geloven.
Evenzeer Hans Jacobs (co-promotor): voor je jarenlange intensieve praktische begeleiding, je meesterlijke vertaling van droge reeksen, getallen en statistische bevindingen tot de voor mij zo gewenste relevante klinische bevindingen, je soms tot in herhaling vallende aanwijzingen en kritieken op de door mij geproduceerde stukken uiteindelijk leidend tot publicatie, je snelle en adequate tekstuele visie, voor je eigenzinnige en faire manier van communicatie.
Met Dick zag ik Hans&Hans als een duet voor twee heren van wetenschappelijke stand. Tijdens de regelmatige bijeenkomsten in Utrecht werd ik steeds op scherp gesteld met als metafoor de Namibische speer die als een machete door mijn epistels werd gehaald.

Marion Wenting-van Wijk, laborant van het Reumalab (hoofd Floris Lafeber), UMCU, voor de ontelbare bepalingen en na-bepalingen, grafieken en statistieken; jouw kunde had ik al meegemaakt bij de promotie van Hans van den Brink waar wij paranimfen waren. Naast een gezellige tijd dreef ik je soms tot wanhoop, knap dat je het dan met mij volhield.
Margriet Huisman, internist, gepromoveerd, alsnog nu bijna reumatoloog, voor het (co-) auteurschap van de artikelen over receptoren en up(s)-en down regulatie; je hebt overzicht over de stof en ik waardeer je kordate optreden.

Ank Jacobs-van Bree voor datamanagement; jij wist eindeloos geduldig en vriendelijk mijn entropische notities om te zetten in bruikbare geordende reeksen op datum.
Gerrie de Kruijf, secretaresse van de afdeling Reumatologie & Klinische Immunologie, UMCU, voor het verwerken van series e-mails, telefoons, printwerk en verzenden en ontvangen van artikelen; Gerrie, dit hoofdstuk hebben we nu afgesloten, zeg dat maar tegen Jeanette.

Het Reum-A-team Deventer en Zutphen: Margreeth Kamphuis, doktersassistente en Diane Oosterbroek (nu reumaconsulent) voor het vanaf het begin liefderijk organiseren van mijn spreekuren, het begeleiden van de patiënten en het eindeloos opzoeken van gegevens en dossiers en de andere leden van het team: Gerrie, Sandra, Christa, Adrie, Anne, Marieke (en destijds Ina); de lunch op maandag blijft heilig.
Gré Hanko, toenmalig secretaresse polikliniek Reumatologie, Utrecht, voor haar warme bejegening en voor het opsporen van zoekgeraakte Sallandsche en Achterhoekse patiënten in het mondaine AZU; vrolijk ondersteund door Ida, Ilse en Chantal.

Cees Haaring, lay-out wizzard, voor je prettige en efficiënte werkwijze; al bij de eerste hoofdstukken bracht jij mijn boek tot leven.

Paul Lamberts, Ben Ploeger en Coen Teunissen, apothekers van het Deventer Ziekenhuis, voor het bereiden, randomiseren en distribueren van de onderzoeks-medicatie.
Dick Hofman, reumatoloog, je kwam graag vanuit Hilversum naar Deventer voor het nauwgezet scoren van de wervelkolomfoto's afgewisseld met gezellige momenten.
Elise Brouwer-Kuiper, radioloog, voor het scoren van de röntgenfoto's van handen en voeten in het laatste jaar van je opleiding buiten de normale werktijden tot 's avonds laat en in het weekend, soms zelfs met dochter.
Ike Nuver-Zwart, reumatoloog in de Maatschap Deventer-Zutphen, voor het includeren van patiënten en voor het stug volhouden dat ik het werk moest afmaken.
Marian Möller, bibliothecaris van de Mediatheek Deventer Ziekenhuis, voor je immer enthousiaste graafwerk op wetenschappelijk terrein en voor het opsporen van de levenswandel van Raoul Dufy, je werd net zo door het verhaal en zijn werk gegrepen als ik.
Bavo Ghuijs (Deventer), Marthijs Berentschot (Zwolle) en Gerrit Berends (Terwolde), jullie zijn mijn lokale software prinsen.

Edwin Beijer en Lenka Kerstens van MSD voor jullie extra en persoonlijke inspanningen o.a. bij het tot stand komen van de buitenkant van dit proefschrift.

Jannes van Everdingen, creatief schrijver, uitgever en broer; een deel van mijn onderwerp hoort ook tot de medische misvattingen.
Diederike van Beuningen, paranimf vanwege lange en bijzondere vriendschap; je staat nu als stuurvrouwe voor mij even aan wal. Hoewel zonder medische achtergrond stelde je vaak rake vragen over mijn onderzoek, dank voor je aanhoudende belangstelling.
Louise van Everdingen voor je aanstekelijke power of life.
Mijn ouders; mijn vader, huidarts, heeft mijn eerste jaren Geneeskunde nog intens meegemaakt; mijn moeder, jij zorgde voor een warm nest en je hebt na het overlijden van Huib het voor elkaar gekregen dat ik mijn studie kon vervolgen.
Mijn kinderen:
Feike, met opgewekte en inventieve energie heb jij je voor mij ingezet rondom de promotie, de man van de org-ideëen.
Wibbien, de krachtige en punctuele wijze waarmee jij je hebt opgeworpen als co-editor bij de afronding van dit boekje vormde een welkom tegenwicht tegen mijn momenten van nonchalance.
Jet, als ik bij jou in Groningen ben voel ik me de meest welkome gast.
Pleun, als het er echt om gaat kan ik op je rekenen en in jouw aanwezigheid voel ik me altijd vrolijk.
Jaap, de ongelooflijke wijze waarop je mij met veel humor en internationaal toneel van het werk kan houden heeft mij er niet van weerhouden dit werk te klaren.
en
Dick, jij bent mijn paradenimf.

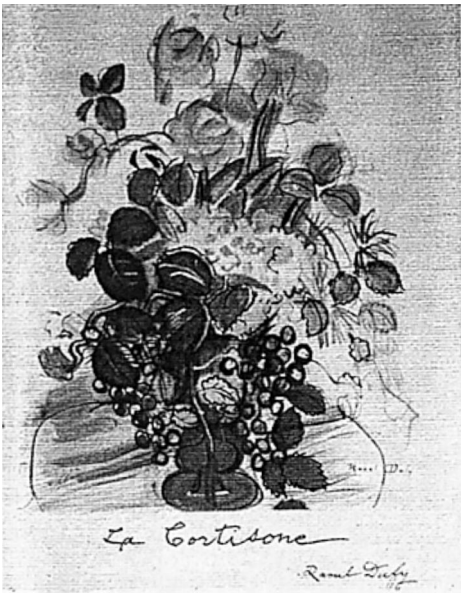
Poem by Raoul Dufy, Paris, April 1950

Yesterday the invitation arrived
Drawing me to Dr Homburger
And his hospital in America
Tomorrow I sail to Boston in search
Of my hands

Forty years ago I painted with Braque
at Estaque
The cubist edges cut too deep into
my palette
And I joined Matisse and became a
Fauve
I covered my canvases only with the
colors that I could feel
Avoiding those that I could see
Unsatisfied I traveled to Munich,
Normandy, Marseille
Saw the terrible women of Avignon
And found myself on the Riviera in
Venice
Fifteen years ago the attacks began
Disfiguring my hands
As if I were painting with leaden
gloves
I sought gold injections
Underwent spinal manipulations
And made a pilgrimage to a Spanish
spa
Yet my hands drew still
I continued studies in my mind
Waiting for the time
When my brush could be awakened
To decorate the canvas
With arabesques and flourishes

I have long tried to capture
The motion of race horses and
regattas
The movement of the orchestra
As musicians chase the notes
In concertos of yellow and red
I have painted electricity
With dynamos and electrons moving
at the speed of light
Craving more speed I released my
canvases
To color silk scarves and dresses
And finally saw my work sail with the
wind
Now my hands are splinted
And I have become disjointed
An old man whose hands will not
obey his heart

Rheumatism loosened Renoirs brush
from his grasp
And his son bound the bristles to the
hollow of his hand
But Dr Perles has assured me
That the new remedy, cortisone and
ACTH
Will release the bonds
Of the arthritis that have held me in
place
My only wish to draw freehand
Following the wind
Flowers that beckon me
And capturing them
In a vase of Anemones


La Cortisone
Raoul Dufy

Curriculum Vitae

Amalia Augusta van Everdingen werd geboren op 21 juni 1947 te Dordrecht. Zij bezocht het Johan de Witt Gymnasium waar zij het diploma Gymnasiumβ behaalde in 1966. Vanaf 1966 studeerde zij Geneeskunde aan de Rijks Universiteit te Leiden alwaar in 1973 het artsexamen werd behaald. Van 1969-1971 was zij werkzaam als kandidaatsassistent op de afdeling Beademing (Drs JJ van Zanten). In 1972 behaalde zij het Amerikaans artsexamen van de Verenigde Staten, het ECFMG (Educational Council for Foreign Medical Graduates), te 's-Gravenhage. Een deel van de co-assistentschappen werd doorlopen in 1973 in Paramaribo, Suriname, waar zij tevens werkzaam was in een leprakolonie. Van 1973-1976 was zij als assistent geneeskundige werkzaam op de afdelingen Longziekten (Prof Dr J Swierenga), Radiologie (Prof Dr AE van Voorthuisen), Radiotherapie (Prof Dr P Thomas) en Heelkunde (Prof Dr M Vink) van het Academisch Ziekenhuis te Leiden. Van 1976-1986 was zij waarnemend huisarts in Noordwijk, Voorhout en Twello. Van 1986 tot heden is zij als arts en wetenschappelijk medewerker verbonden aan de afdeling Reumatologie van het Deventer Ziekenhuis te Deventer en die van het Gelre Ziekenhuis te Zutphen (Drs DR Siewertsz van Reesema en Drs HH Nuver-Zwart, reumatologen) en vanaf 1989 tevens aan de afdeling Reumatologie en Klinische Immunologie van het Universitair Medisch Centrum Utrecht (Prof Dr JWJ Bijlsma) waar zij vanaf 1992, mede dankzij subsidie van het Nationaal Reumafonds, in staat is wetenschappelijk onderzoek te verrichten oa. naar de invloed van glucocorticoïden bij de behandeling van vroege reumatoide artritis.
Zij ondersteunt de kliniek Ndlovu Medical Center (NMC) van Drs H Tempelman en Drs P Schrooder, huisartsen te Elandsdoorn, Mpumalanga, Zuid Afrika.