Analyses of similarities and differences in glucocorticoid therapy between rheumatoid arthritis and ankylosing spondylitis – a systematic comparison

C.M. Spies, G.-R. Burmester, F. Buttgereit

Department of Rheumatology and Clinical Immunology, Charité University Hospital, Berlin, Germany.

Cornelia M. Spies, MD
Gerd-Rüdiger Burmester, PhD, Professor
Frank Buttgereit, MD, Professor

Please address correspondence to:
Dr. C. M. Spies,
Department of Rheumatology and Clinical Immunology,
Charité University Hospital,
Campus Mitte, Charitéplatz 1,
10117 Berlin, Germany.
E-mail: cornelia.spies@charite.de

Received and accepted on July 29, 2009.

Clin Exp Rheumatol 2009; 27 (Suppl. 55): S152-S158.

Key words: Ankylosing spondylitis, rheumatoid arthritis, glucocorticoid, treatment, glucocorticoid resistance, glucocorticoid receptor, membrane glucocorticoid receptor.

Competing interests: none declared.

ABSTRACT

Glucocorticoids (GCs) have powerful and potent anti-inflammatory and immunomodulatory effects and are widely established in regard to the treatment of rheumatism and other diseases. In rheumatoid arthritis (RA), GCs are used systemically at several different dosages and/or local (intraarticular) therapy. They have been shown to exert strong short-term anti-inflammatory effects but also long-term positive effects on radiographic progression of the disease. In comparison, patients with ankylosing spondylitis (AS) are considered to be less responsive to GC therapy than patients with RA, although controlled studies on the effects of low-dose GCs in AS are lacking. In AS, GCs are mainly used for local therapy and occasionally for systemic pulse therapy only. The underlying mechanisms for these differences are unclear. GCs act on primary and secondary immune cells via different mechanisms of action: cytosolic GC receptor (cGCR)-mediated genomic and non-genomic effects, membrane-bound GC receptor (mGCR)-mediated non-genomic effects and – as achieved at very high concentrations – non-specific non-genomic effects. The phenomenon of GC resistance is also known in RA. Several different mechanisms may mediate this phenomenon; among them are alterations in number, binding affinity or phosphorylation status of the GCR, polymorphic changes and/or over-expression of chaperones/co-chaperones, increased expression of inflammatory transcription factors, the multidrug resistance pump, over-expression of the GCR beta isoform, alteration in the expression of mGCR and imbalance of 11beta-hydroxysteroid dehydrogenase type 1 & 2 activity. Translation of insights on GC action and resistance obtained in RA to AS may contribute to a better understanding of the pathophysiology of both diseases.

Introduction

Glucocorticoids (GCs) are powerful drugs with strong anti-inflammatory and immunomodulatory effects that are used to treat inflammatory diseases (1). Treatment with GCs in rheumatic diseases was employed for the first time by Hench and his colleagues in patients with rheumatoid arthritis (RA). He had noticed over years of subtle observations that the activity of RA improved considerably when patients with RA were coincidentally diseased with jaundice or when female patients became pregnant (2). He concluded that there has to be an "anti-rheumatic factor" which is "neither a product of the liver nor a unisexual hormone" (2). These analyses finally led to the application of synthesised cortisone (Compound E). In September 1948, a female patient with severe RA was treated with cortisone for the first time. The patient status improved dramatically and further patients were then treated as well. After publication of the results (3), the use of GCs spread out over the whole field of rheumatology. The first reports mentioning GCs in ankylosing spondylitis (AS) date back to 1949/50 (4).

Nowadays, GCs are widely established in the treatment of RA. As estimated from baseline data of early studies with anti-TNF agents and other agents, 56-68% of the patients having RA are treated more or less continuously with GCs (5-9). This is in contrast to only 10-25% of the patients with AS (10-12). The German collaborative arthritis centres database registered a current treatment with low dose GC therapy (up to 7.5 mg/day) in 49.7% of the RA patients in comparison to only 15.6% of the AS patients (13). Medium and high dose GC therapy (>7.5 mg/day) was uncommon in both diseases (7.0% of RA patients and 3.2% of AS patients, respectively) (13). Another

analysis found that more than 90% of RA patients were taking one or more disease modifying antirheumatic drugs (DMARDs), demonstrating that GCs are administered mainly as an additional therapy in RA. The frequency of patients taking GCs diminished to one half after one year of taking biological agents indicating that GC therapy is often used as a bridging therapy (7).

In this review, we will address the similarities and differences between RA and AS in regard to treatment with GCs. The discrepancy that patients with AS are in general obviously less responsive to GC therapy than are patients with RA is – according to Braun and Sieper – indeed "fascinating" (14). However, it is somewhat surprising that the reasons for this difference, 60 years after the introduction of GCs into the treatment of rheumatic diseases, remain completely unclear. We summarise the present knowledge on GC therapy in RA and AS under the aspects of clinical efficacy and mechanisms of GC actions and resistance.

Low dose GC therapy

In RA, a survey of 10 studies involving 320 patients provided strong evidence of a short-term benefit of low dose GCs (≤15 mg per day), with a large effect size of 1.75 on pain (15). The longer-term benefit of low-dose GCs in RA is less impressive – a review of 7 studies evaluating the symptomatic effect of GC in RA concluded that, when administered for a period of approximately 6 months, they had an effect size for pain of only 0.43 (16). Improvement has been documented in all clinical parameters, including pain-scales, joint scores, morning stiffness and fatigue, but also in parameters of the acute phase reaction, such as ESR and CRP. After 6 months of therapy, the beneficial effects of GC in general seem to diminish. Nevertheless, many clinicians report that if this therapy is then tapered off and terminated, patients experience an aggravation of symptoms. It appears that many patients can be treated effectively with initial prednisone doses of <5 mg/day, resulting in improvement in function and pain comparable to that seen at higher doses (17).

In AS, not even one controlled study has been performed in order to test the efficacy of systemic GCs. According to Braun and Sieper, uncontrolled clinical experience suggests that, in contrast to RA, systemic GCs in general are not effective very well for symptoms and structural damage in AS, at least when applied in low and moderate dosages (14). However, there may be subgroups of patients who respond better than others: those with peripheral arthritis, anterior uveitis, concurrent inflammatory bowel disease, elevated concentrations of C-reactive protein or those who are negative for human leukocyte antigen (HLA) B27 (14, 18, 19).

The mechanisms of joint inflammation in RA differ from the mechanisms of joint destruction (20). Kirwan *et al.* compared patients with early RA (less than 2 years from diagnosis) proceeding with a disease-modifying therapy together with prednisolone 7.5 mg daily, or with a placebo (21, 22). The difference between the groups for the articular index in favour of the GC was significant at 3 months only. However, the difference between the groups for radiographic progression, as measured by the Larsen score, was significant at 1, 2 and 3 years. Therefore, x-ray progression is reduced by low dose prednisolone, and while clinical symptoms on the average do not change after prednisolone is discontinued (although some patients may experience flare), x-ray progression is resumed (22). In 2007, a large systematic evidence-based literature search according to the Cochrane Collaboration recommendations included 15 studies and 1,414 patients (23). The majority of trials studied early RA (disease duration up to 2 years). All studies except one showed a numerical treatment effect in favour of GCs. The authors concluded that even under the most conservative of estimates, the evidence is convincing that GCs given in addition to standard therapy can substantially reduce the rate of erosion progression in rheumatoid arthritis (23). Furthermore, medium term follow-ups of two studies have been reported which raise the possibility that GC may have enduring or even permanent effects on disease progression long after therapy with GCs had been discontinued. During the 4-5 year follow up period of the COBRA regimen, when GC treatment had been discontinued, the x-ray progression rate measured by the Sharp index progression rate was 8.6 points per year in those not treated with GCs during the original study, but it was only 5.6 in the patients who had previously been treated with GCs (24, 25). In the Utrecht trial patients had been treated with 10 mg prednisolone daily or a placebo for 2 years. During the additional 3 years of follow-up, radiographic scores showed significantly less progression in the original prednisone group than in the original placebo group. Indeed, in this study the reduced rate of progression was greater than 70% (26, 27). Another work demonstrated little radiographic progression in most patients treated with long-term GC (28). Thus, today GC can be considered to have disease modifying properties *in early RA* and in combination with other drugs and may thus be referred to as DMARDs (29). It has not yet been established, however, whether or not GC can also inhibit progression of erosions in *RA of longer duration*. To our knowledge, there is no evidence concerning the effect of GC therapy on radiologic progression in AS.

GC pulse therapy

"Pulse therapy" is considered to be a specific therapeutic entity that refers to the administration of ≥250 mg prednisone equivalent per day (usually i.v.) for a short period of time (usually one to ≤5 days). There are several studies on the effects of pulse therapy in both diseases. In RA, GC pulse therapy is applied to treat some serious complications of the disease and to induce remission in active disease, often in the initiation phase of second-line antirheumatic treatment. Among the latter patients, pulse therapy with regimens of 1000 mg methylprednisolone (MP) intravenously, 200 mg dexamethasone or other equivalent doses, for one or several days, has proven to be effective in several studies (30-32); here, the beneficial effect generally lasts for about 6 weeks, with large variations in duration. Pulse MP has been

shown to have strong and rapid inhibitory effects on proinflammatory mediators in peripheral blood, synovial fluid, and the synovial membrane in RA (33, 34). However, in contrast to oral GCs, monthly intramuscular treatment with 120 mg depot methylprednisolone acetate had only a small effect on erosion progression (35). Also intravenous MP plus methotrexate has been shown to have a lower effect on erosion progression than treatment with infliximab plus methotrexate in RA, however the remission rates were similar (36).

In AS, there is also some evidence for a strong therapeutic effect of intravenous methylprednisolone pulse therapy in a few single observations and open studies in cases of severe, active AS (37-40). Therefore, the efficacy of GC pulse therapy seems to be similar in RA and AS, indicating a different mechanism of GC action (see below) at higher doses of GC therapy.

Intraarticular GC therapy

Intraarticular GC injection therapy is established in RA and AS. Similar to systemic pulse therapy, in intraarticular therapy very high GC concentrations can be achieved (locally). Intraarticular GCs are often used in RA, even though few data are available on the positive short-term effects of intraarticular GC administration in relieving local symptoms of inflammation (41, 42). In AS, intraarticular GCs have been shown to induce short-term improvement in peripheral arthritis including disease of the hips (43), and sacroiliitis (44, 45). In the sacroiliac joints, the effect of computed-tomography-guided injections seems to last longer than that of the blind periarticular injection technique, which is also feasible (46). Similar benefit was reported in another study employing dynamic MRI guidance (47). To our knowledge, there have been no high quality clinical studies published on the efficacy of intraarticular GCs on peripheral arthritis or enthesitis in AS.

Modified-release GC therapy

For RA, it has recently been hypothesised that the best time point to apply immunosuppressive therapy is during the initial phase of a pro-inflammatory response (*i.e.* not in the turning-off phase) (48). Indeed, a recent study demonstrated that a newly developed drug, modified-release prednisone, is clinically and statistically more effective than the conventional immediate-release prednisone preparation in regard to morning stiffness of the joints. This new formulation releases prednisone about 4 h after ingestion – *i.e.* at about 02:00 o'clock if given at bedtime (49). The 12-month data of the study show a significantly greater and sustained efficacy in reduction of morning stiffness and IL-6 levels, combined with a favourable safety profile (50). For AS, the data available appear to be too scarce to speculate about any possible advantages of a time-adapted therapy (Spies *et al.*, unpublished data).

Mechanisms of GC action

GCs induce their anti-inflammatory and immunosuppressive effects through different mechanisms targeting a variety of immune cells. Almost all primary and secondary immune cells are more or less affected. A selection of the most important effects on the different cell types is listed in Table I (1).

On the cellular level, the clinical actions can be summarised as follows (1):

- GCs inhibit leukocyte traffic and access of leukocytes to the site of inflammation
- GCs interfere with functions of leukocytes, fibroblasts and endothelial cells
- GCs suppress the production and actions of humoral factors involved in the inflammatory process.

For the underlying molecular mechanisms, four different mechanisms have been identified to date (51):

Most of the desired anti-inflammatory effects are mediated by *"cGCR-mediated classical genomic effects"*. In the cytosol GC, molecules bind to ubiquitously expressed cytosolic GC receptors (cGCRs). The activated GC/GCR-complexes cause either an up or a down-regulation of the synthesis of certain proteins via binding to specific DNA-binding sites (GC-responsive elements) or they negatively interfere with transcription factors such as nuclear factor-kappaB (NF-kappaB) and activator protein-1 (AP-1) (52). By this latter pathway, GCs down-regulate the synthesis of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumour necrosis factor alpha (TNF-α), key players in the process of joint inflammation in RA. Also the retardation of radiological progression in RA is probably mediated by this mechanism, as IL-1 and TNF-α stimulate production of the receptor activator of nuclear factor kappa B ligand (RANKL) which finally leads to more activated osteoclasts, responsible for bone resorption and erosions in RA (53). As TNF-α is also a key player in AS, it can be speculated that in AS, GC actions might be somewhat diminished at the pre-receptor or receptor level or there are specific interferences (see below).

Secondly, the GC/GCR multiprotein complex also releases chaperones and co-chaperones such as Src, which themselves have been shown to cause rapid effects, termed *cGCR-mediated non-genomic effects* (1, 51).

Table I. Important effects of GCs on primary and secondary immune cells (1).

Monocytes/macrophages	number of circulating cells ↓ (myelopoiesis ↓, release ↓) expression of MHC class II molecules and Fc receptors ↓ synthesis of pro-inflammatory cytokines (*e.g.* IL-2, IL-6, TNF-α) and prostaglandins ↓
T cells	number of circulating cells (redistribution effects) ↓ production and action of IL-2 ↓ (most important)
Granulocytes	number of eosinophile and basophile granulocytes ↓ number of circulating neutrophils ↑
Endothelial cells	vessel permeability ↓ expression of adhesion molecules ↓ production of IL-1 and prostaglandins ↓
Fibroblasts	proliferation ↓ production of fibronectin and prostaglandins ↓

Thirdly, it has been suggested that GCs also mediate non-genomic effects via membrane-bound GCRs (mGCRs), so-called *mGCR-mediated non-genomic effects* (1, 51). mGCRs have been found on monocytes and B-cells in patients with RA and AS (54, 55). In RA, a strong positive correlation of mGCR expression on monocytes to parameters of disease activity was found (54). In contrast, in AS a correlation of mGCR expression and disease activity could not be shown (55). However, the functional relevance of these receptors could not yet be demonstrated. Therefore it is unclear and speculative, whether the different expression of mGCRs might contribute to the differences in the clinical response to GC treatment between RA and AS. Other recent work has demonstrated a membrane-linked GCR on human T-cells. It was shown that GC treatment rapidly disrupts T-cell receptor (TCR)-linked GCR multiprotein complexes, associated with a cellular redistribution of Lck and Fyn kinases, finally leading to an impaired TCR signalling (56, 57). The relevance of these effects on diseases like RA and AS is unclear; however, T-cells are important effector cells in both diseases.

Finally, GCs at high concentrations are able to intercalate into cellular membranes, such as plasma and mitochondrial membrane, and change their properties (58). This is the basis for *non-specific non-genomic effect*s, possibly mediated by changes in the cation transport through the plasma membranes and in the proton leak of mitochondria. These physicochemical interactions with biological membranes most likely represent the key to the very rapid immunosuppressive and anti-inflammatory effects of high-dose GCs (51, 58, 59). Very high GC concentrations are achieved by intraarticular GC injections or intravenous GC pulse therapy.

In clinical practice, for RA and other diseases, higher GC dosages are used with increasing clinical activity and greater severity of the disease under treatment. In AS, as has been shown, only pulse therapy and intraarticular therapy are effective. There is now a more scientific rationale for this (mostly successful) empirical clinical approach (51): (i) GCR saturation is increased in a dose-dependent manner (up to a limit), which intensifies the therapeutically relevant, *genomic* GC actions. (ii) It is now thought that with further dosage increases, the additional and qualitatively different, *non-specific, non-genomic* actions of GCs come into play increasingly. The relation of cellular GC actions and the clinical response in RA and AS is summarised in Table II. This table also contains a column on the so-called *cGCR-mediated non-genomic actions*, but there is currently only scattered information on dose-effect relationships. Table II does not mention *specific non-genomic actions via mGCR* that have been recognised, for the simple reason that their functional relevance remains unclear.

GC resistance

As already mentioned above, there exists the clinical observation that RA patients respond well to GC treatment, whereas AS patients respond badly. Thus, also the question of susceptibility for GCs should be discussed, as this will lead to the problem of GC resistance in RA.

The phenomenon of GC resistance, manifested by the absence of an expected response to treatment, is also known for RA and other inflammatory diseases, such as asthma, Crohn's disease and ulcerative colitis and occurs in about 30% of the patients (1, 60). GC resistance in RA has not been well defined. Usually, waning of symptomatic relief has been considered to be a sign of GC resistance. Recently, Sliwinska-Stanczyk *et al*. demonstrated that that in patients with active RA treated with daily intravenous doses of 20 mg methylprednisolone for 2 weeks, GC resistance occurred in about 25% of the patients (61). They used a definition of GC resistance based on the changes used in the European League Against Rheumatism (EULAR) response criteria (62). For patients with an initial DAS score of 5.1 or less, a reduction of less than 0.6 was considered to be GC resistant. For patients with an initial DAS score of greater than 5.1, a reduction of less than 1.2 was considered to be GC resistant. Eleven out of 44 patients showed no response according to these criteria. Furthermore, a clear distinction could be made between GC-sensitive and GC-resistant patients in the methylprednisolone-induced inhibition of the proliferatory response of peripheral blood mononuclear cells

Table II. Relationship between cellular GC actions and GC response in RA and AS (modified according to (51)).

Terminology [mg prednisone equivalent per day]	Clinical application	Genomic actions [receptor saturation]	Unspecific non-genomic actions	cGCR-mediated non-genomic actions	Clinical experience in RA	Clinical experience in AS
Low dose [≤7.5]	Maintenance therapy	+ [<50%]	–	?	Good response Effect on erosion progression	No response (?)
Medium dose [>7.5 - ≤30]	Initial therapy	++ [>50 - <100%]	(+)	(+)	Good response (in first 6 months)	No response (?)
Pulse therapy [≥250 mg for one or a few days]	Severe exacerbations	+++ [100%]	+++	+(++?)	Good response No effect on erosion progression	
Intraarticular therapy	Acute or refractory synovitis	+++ [100%]	+++	+(++?)		Good response

Table III. Potential mechanisms mediating GC resistance.

Mechanism	References
Alterations in number (induced for example by inflammation, hormones, non-steroidal anti-rheumatic drugs or GC treatment itself), binding affinity or phosphorylation status of the GCR	(65-70)
Polymorphic changes and/or over-expression of chaperones/ co-chaperones (such as kinases of the mitogen-activated protein kinase (MAPK) system)	(71, 72)
Increased expression of inflammatory transcription factors (such as AP-1 and NF-kappaB, induced by large amounts of pro-inflammatory cytokines in very active inflammation)	(73, 74)
Multidrug resistance pump (MDR1) (which can actively extrude GCs)	(75)
Overexpression of GCR beta (a splice variant and dominant negative inhibitor of GCR alpha)	(76, 77)
Alteration in the expression of mGCRs	(54, 55)
Imbalance in 11beta-hydroxysteroid dehydrogenase type 1&2 activity	(78)

acquired from these patients achieving 100% positive and 100% negative predictive values (61).

What is the molecular basis for GC resistance? It should be mentioned that also hereditary and acquired GCR mutations exist, such as the so-called familial/sporadic GC resistance, a rare condition recently defined as being a generalised, partial, target-tissue insensitivity to GCs (63). Acquired mutations in the GCR gene due to therapy or selection have been observed in hematological diseases (64). For rheumatic diseases, genome analysis up to now has failed to show any GCR gene alterations. Several different mechanisms may mediate this phenomenon. Potential mechanisms for GC resistance are summarised in Table III.

It is somewhat surprising that only very few data are available on the phenomenon of GC resistance in AS. Lee et al. investigated the expression of GCR beta mRNA in untreated patients with AS and RA. They found the expression of GCR beta mRNA in AS to be enhanced when compared with that of RA and controls (79). The level of cGCR beta mRNA expression was apparently not related to the inflammatory markers or disease activity scores in RA and AS patients, a finding which suggests that it is not induced by the inflammatory reaction. To our knowledge, no other specific investigations have been carried out in this regard.

Conclusions

(i) Yes, a difference between RA and AS is present for low and medium dosed GC therapy.

(ii) Low and medium dosed GCs reduce inflammation and radiographic progression in RA, but have no effects in AS (however, no studies appear to have been undertaken here).

(iii) The reason for this difference is unclear. However, very high GC doses are similarly effective in both diseases. We discuss that these effects may be due to non-genomic actions.

(iv) The phenomenon of GC resistance is potentially important for sure, but further investigations are nonetheless necessary (basic science and clinical research).

References

1. BUTTGEREIT F, SAAG KG, CUTOLO M, DA SILVA JA, BIJLSMA JW: The molecular basis for the effectiveness, toxicity, and resistance to glucocorticoids: focus on the treatment of rheumatoid arthritis. *Scand J Rheumatol* 2005; 34: 14-21.
2. HENCH PS: Potential reversibility of rheumatoid arthritis. *Ann Rheum Dis* 1949; 8: 90-6.
3. HENCH PS, KENDALL EC *et al*.: The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone; compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. *Mayo Clin Proc* 1949; 24: 181-97.
4. BOLAND EW: The effects of cortisone and adrenocorticotropic hormone (ACTH) on certain rheumatic diseases. *Calif Med* 1950; 72: 405-14.
5. FLEISCHMANN RM, SCHECHTMAN J, BENNETT R *et al*.: Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. *Arthritis Rheum* 2003; 48: 927-34.
6. MORELAND LW, SCHIFF MH, BAUMGARTNER SW *et al*.: Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med* 1999; 130: 478-86.
7. THIELE K, BUTTGEREIT F, HUSCHER D, ZINK A: Current use of glucocorticoids in patients with rheumatoid arthritis in Germany. *Arthritis Rheum* 2005; 53: 740-7.
8. WEINBLATT ME, KREMER JM, COBLYN JS *et al*.: Pharmacokinetics, safety, and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. *Arthritis Rheum* 1999; 42: 1322-8.
9. ZINK A, LISTING J, NIEWERTH M, ZEIDLER H: The national database of the German Collaborative Arthritis Centres: II. Treatment of patients with rheumatoid arthritis. *Ann Rheum Dis* 2001; 60: 207-13.
10. CALIN A, DIJKMANS BA, EMERY P *et al*.: Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. *Ann Rheum Dis* 2004; 63: 1594-600.
11. DAVIS JC, JR., VAN DER HEIJDE D, BRAUN J *et al*.: Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003; 48: 3230-6.
12. GORMAN JD, SACK KE, DAVIS JC, JR.: Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. *N Engl J Med* 2002; 346: 1349-56.
13. ZINK A, THIELE K, HUSCHER D *et al*.: Healthcare and burden of disease in psoriatic arthritis. A comparison with rheumatoid arthritis and ankylosing spondylitis. *J Rheumatol* 2006; 33: 86-90.
14. BRAUN J, SIEPER J: Therapy of ankylosing spondylitis and other spondyloarthritides: established medical treatment, anti-TNF-alpha therapy and other novel approaches. *Arthritis Res* 2002; 4: 307-21.
15. GOTZSCHE PC, JOHANSEN HK: Meta-analysis of short-term low dose prednisolone versus placebo and non-steroidal anti-inflammatory drugs in rheumatoid arthritis. *Bmj* 1998; 316: 811-8.
16. CRISWELL LA, SAAG KG, SEMS KM *et al*.: Moderate-term, low-dose corticosteroids for rheumatoid arthritis. *Cochrane Database Syst Rev* 2000: CD001158.
17. PINCUS T, SWEARINGEN C: Prednisone in initial doses less than 5 mg/day is as efficacious as larger doses in patients with rheumatoid arthritis (RA). *Ann Rheum Dis* 2009; 68 (Suppl. 3): 593.
18. MERCADO U: The use of methylprednisolone pulse therapy in a severe case of HLA-B27 negative ankylosing spondylitis. *J Rheumatol* 1994; 21: 1582-3.
19. YOSHIDA S, MOTAI Y, HATTORI H, YOSHIDA H, TORIKAI K: A case of HLA-B27 negative ankylosing spondylitis treated with methylprednisolone pulse therapy. *J Rheumatol* 1993; 20: 1805-6.

20. KIRWAN JR: The synovium in rheumatoid arthritis: evidence for (at least) two pathologies. *Arthritis Rheum* 2004; 50: 1-4.
21. 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.
22. 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.
23. KIRWAN JR, BIJLSMA JW, BOERS M, SHEA BJ: Effects of glucocorticoids on radiological progression in rheumatoid arthritis. *Cochrane Database Syst Rev* 2007: CD006356.
24. BOERS M, VERHOEVEN AC, MARKUSSE HM *et al*.: Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997; 350: 309-18.
25. LANDEWÉ RB, 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.
26. JACOBS JW, VAN EVERDINGEN AA, VERSTAPPEN SM, BIJLSMA JW: Followup radiographic data on patients with rheumatoid arthritis who participated in a two-year trial of prednisone therapy or placebo. *Arthritis Rheum* 2006; 54: 1422-8.
27. 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 randomized, double-blind, placebo-controlled clinical trial. *Ann Intern Med* 2002; 136: 1-12.
28. PINCUS T, SOKKA T, KAUTIAINEN H: Patients seen for standard rheumatoid arthritis care have significantly better articular, radiographic, laboratory, and functional status in 2000 than in 1985. *Arthritis Rheum* 2005; 52: 1009-19.
29. BIJLSMA JW, HOES JN, VAN EVERDINGEN AA, VERSTAPPEN SM, JACOBS JW: Are glucocorticoids DMARDs? *Ann N Y Acad Sci* 2006; 1069: 268-74.
30. JACOBS JW, GEENEN R, EVERS AW, VAN JAARSVELD CH, KRAAIMAAT FW, BIJLSMA JW: 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.
31. NOSSENT HC, BAKLAND G, ASLAKSEN HK, OLSEN G, NORDVAG BY: Efficacy of methylprednisolone pulse therapy versus infliximab in the treatment of severe flares of chronic polyarthritis. *Scand J Rheumatol* 2001; 30: 335-9.
32. WENTING-VAN WIJK MJ, BLANKENSTEIN MA, LAFEBER FP, BIJLSMA JW: Relation of plasma dexamethasone to clinical response. *Clin Exp Rheumatol* 1999; 17: 305-12.
33. BERTOUCH JV, ROBERTS-THOMSON PJ, SMITH MD, WOODRUFF TG, BROOKS PM, BRADLEY J: Methylprednisolone infusion therapy in rheumatoid arthritis patients. The effect on synovial fluid lymphocyte subsets and inflammatory indices. *Arthritis Rheum* 1986; 29: 32-8.
34. YOUSSEF PP, TRIANTAFILLOU S, PARKER A *et al*.: Effects of pulse methylprednisolone on cell adhesion molecules in the synovial membrane in rheumatoid arthritis. Reduced E-selectin and intercellular adhesion molecule 1 expression. *Arthritis Rheum* 1996; 39: 1970-9.
35. CHOY EH, KINGSLEY GH, KHOSHABA B, PIPITONE N, SCOTT DL: A two year randomised controlled trial of intramuscular depot steroids in patients with established rheumatoid arthritis who have shown an incomplete response to disease modifying antirheumatic drugs. *Ann Rheum Dis* 2005; 64: 1288-93.
36. DUREZ P, MALGHEM J, NZEUSSEU TOUKAP A *et al*.: Treatment of early rheumatoid arthritis: a randomized magnetic resonance imaging study comparing the effects of methotrexate alone, methotrexate in combination with infliximab, and methotrexate in combination with intravenous pulse methylprednisolone. *Arthritis Rheum* 2007; 56: 3919-27.
37. EJSTRUP L, PETERS ND: Intravenous methylprednisolone pulse therapy in ankylosing spondylitis. *Dan Med Bull* 1985; 32: 231-3.
38. MINTZ G, ENRIQUEZ RD, MERCADO U, ROBLES EJ, JIMENEZ FJ, GUTIERREZ G: Intravenous methylprednisolone pulse therapy in severe ankylosing spondylitis. *Arthritis Rheum* 1981; 24: 734-6.
39. PETERS ND, EJSTRUP L: Intravenous methylprednisolone pulse therapy in ankylosing spondylitis. *Scand J Rheumatol* 1992; 21: 134-8.
40. RICHTER MB, WOO P, PANAYI GS, TRULL A, UNGER A, SHEPHERD P: The effects of intravenous pulse methylprednisolone on immunological and inflammatory processes in ankylosing spondylitis. *Clin Exp Immunol* 1983; 53: 51-9.
41. CONAGHAN PG, O'CONNOR P, MCGONAGLE D *et al*.: Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis. *Arthritis Rheum* 2003; 48: 64-71.
42. PROUDMAN SM, CONAGHAN PG, RICHARDSON C *et al*.: Treatment of poor-prognosis early rheumatoid arthritis. A randomized study of treatment with methotrexate, cyclosporin A, and intraarticular corticosteroids compared with sulfasalazine alone. *Arthritis Rheum* 2000; 43: 1809-19.
43. PLANT MJ, BORG AA, DZIEDZIC K, SAKLATVALA J, DAWES PT: Radiographic patterns and response to corticosteroid hip injection. *Ann Rheum Dis* 1997; 56: 476-80.
44. BRAUN J, BOLLOW M, SEYREKBASAN F *et al*.: Computed tomography guided corticosteroid injection of the sacroiliac joint in patients with spondyloarthropathy with sacroiliitis: clinical outcome and followup by dynamic magnetic resonance imaging. *J Rheumatol* 1996; 23: 659-64.
45. MAUGARS Y, MATHIS C, BERTHELOT JM, CHARLIER C, PROST A: Assessment of the efficacy of sacroiliac corticosteroid injections in spondylarthropathies: a double-blind study. *Br J Rheumatol* 1996; 35: 767-70.
46. LUUKKAINEN R, NISSILA M, ASIKAINEN E *et al*.: Periarticular corticosteroid treatment of the sacroiliac joint in patients with seronegative spondylarthropathy. *Clin Exp Rheumatol* 1999; 17: 88-90.
47. GUNAYDIN I, PEREIRA PL, DAIKELER T *et al*.: Magnetic resonance imaging guided corticosteroid injection of the sacroiliac joints in patients with therapy resistant spondyloarthropathy: a pilot study. *J Rheumatol* 2000; 27: 424-8.
48. STRAUB RH, CUTOLO M: Circadian rhythms in rheumatoid arthritis: implications for pathophysiology and therapeutic management. *Arthritis Rheum* 2007; 56: 399-408.
49. BUTTGEREIT F, DOERING G, SCHAEFFLER A *et al*.: Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. *Lancet* 2008; 371: 205-14.
50. BUTTGEREIT F, DOERING G, SCHAEFFLER A, WITTE S, SZECHINSKI J, ALTEN R: 12-month safety and efficacy data of night time release prednisone: sustained reduction of morning stiffness and IL-6 combined with favorable safety profile for treatment in rheumatoid arthritis. *Ann Rheum Dis* 2009; 68 (Suppl. 3): 133.
51. BUTTGEREIT F, STRAUB RH, WEHLING M, BURMESTER GR: Glucocorticoids in the treatment of rheumatic diseases: an update on the mechanisms of action. *Arthritis Rheum* 2004; 50: 3408-17.
52. ALMAWI WY, MELEMEDJIAN OK: Molecular mechanisms of glucocorticoid antiproliferative effects: antagonism of transcription factor activity by glucocorticoid receptor. *J Leukoc Biol* 2002; 71: 9-15.
53. FEUERHERM AJ, BORSET M, SEIDEL C *et al*.: Elevated levels of osteoprotegerin (OPG) and hepatocyte growth factor (HGF) in rheumatoid arthritis. *Scand J Rheumatol* 2001; 30: 229-34.
54. BARTHOLOME B, SPIES CM, GABER T *et al*.: Membrane glucocorticoid receptors (mGCR) are expressed in normal human peripheral blood mononuclear cells and up-regulated after in vitro stimulation and in patients with rheumatoid arthritis. *Faseb J* 2004; 18: 70-80.
55. TRYC AB, SPIES CM, SCHNEIDER U *et al*.: Membrane glucocorticoid receptor expression on peripheral blood mononuclear cells in patients with ankylosing spondylitis. *J Rheumatol* 2006; 33: 2249-53.
56. LOWENBERG M, TUYNMAN J, BILDERBEEK J *et al*.: Rapid immunosuppressive effects of glucocorticoids mediated through Lck and Fyn. *Blood* 2005; 106: 1703-10.
57. LOWENBERG M, VERHAAR AP, BILDERBEEK J *et al*.: Glucocorticoids cause rapid dissociation of a T-cell-receptor-associated protein complex containing LCK and FYN. *EMBO Rep* 2006; 7: 1023-9.
58. BUTTGEREIT F, SCHEFFOLD A: Rapid glucocorticoid effects on immune cells. *Steroids* 2002; 67: 529-34.
59. BUTTGEREIT F, DA SILVA JA, BOERS M *et al*.:

Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. *Ann Rheum Dis* 2002; 61: 718-22.

60. KIRWAN JR: Glucocorticoid resistance in patients with rheumatoid arthritis. *Scand J Rheumatol* 2007; 36: 165-6.
61. SLIWINSKA-STANCZYK P, PAZDUR J, ZIOLKOWSKA M, JAWORSKI J, KAMINSKA-TCHORZEWSKA E, LACKI JK: The effect of methylprednisolone on proliferation of PBMCs obtained from steroid-sensitive and steroid-resistant rheumatoid arthritis patients. *Scand J Rheumatol* 2007; 36: 167-71.
62. VAN GESTEL AM, PREVOO ML, VAN 'T HOF MA, VAN RIJSWIJK MH, VAN DE PUTTE LB, VAN RIEL PL: Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. *Arthritis Rheum* 1996; 39: 34-40.
63. CHARMANDARI E, KINO T, ICHIJO T, CHROUSOS GP: Generalized glucocorticoid resistance: clinical aspects, molecular mechanisms, and implications of a rare genetic disorder. *J Clin Endocrinol Metab* 2008; 93: 1563-72.
64. SCHMIDT S, RAINER J, PLONER C, PRESUL E, RIML S, KOFLER R: Glucocorticoid-induced apoptosis and glucocorticoid resistance: molecular mechanisms and clinical relevance. *Cell Death Differ* 2004; 11 (Suppl. 1): S45-55.
65. FREY FJ, HORBER FF, FREY BM: Altered metabolism and decreased efficacy of prednisolone and prednisone in patients with hyperthyroidism. *Clin Pharmacol Ther* 1988; 44: 510-21.
66. PELLETIER JP, DiBATTISTA JA, RANGER P, MARTEL-PELLETIER J: The reduced expression of glucocorticoid receptors in synovial cells induced by nonsteroidal antiinflammatory drugs can be reversed by prostaglandin E1 analog. *J Rheumatol* 1994; 21: 1748-52.
67. HUISMAN AM, VAN EVERDINGEN AA, WENTING MJ *et al*.: Glucocorticoid receptor downregulation in early diagnosed rheumatoid arthritis. *Ann N Y Acad Sci* 2002; 966: 64-7.
68. 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.
69. 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: 1127-31.
70. SCHLAGHECKE R, KORNELY E, WOLLENHAUPT J, SPECKER C: Glucocorticoid receptors in rheumatoid arthritis. *Arthritis Rheum* 1992; 35: 740-4.
71. KANG KI, MENG X, DEVIN-LECLERC J *et al*.: The molecular chaperone Hsp90 can negatively regulate the activity of a glucocorticosteroid-dependent promoter. *Proc Natl Acad Sci U S A* 1999; 96: 1439-44.
72. KULLMANN M, SCHNEIKERT J, MOLL J *et al*.: RAP46 is a negative regulator of glucocorticoid receptor action and hormone-induced apoptosis. *J Biol Chem* 1998; 273: 14620-5.
73. CHIKANZA IC, KOZACI DL: Corticosteroid resistance in rheumatoid arthritis: molecular and cellular perspectives. *Rheumatology* (Oxford) 2004; 43: 1337-45.
74. MEDURI GU, YATES CR: Systemic inflammation-associated glucocorticoid resistance and outcome of ARDS. *Ann N Y Acad Sci* 2004; 1024: 24-53.
75. MAILLEFERT JF, MAYNADIE M, TEBIB JG *et al*.: Expression of the multidrug resistance glycoprotein 170 in the peripheral blood lymphocytes of rheumatoid arthritis patients. The percentage of lymphocytes expressing glycoprotein 170 is increased in patients treated with prednisolone. *Br J Rheumatol* 1996; 35: 430-5.
76. YUDT MR, JEWELL CM, BIENSTOCK RJ, CIDLOWSKI JA: Molecular origins for the dominant negative function of human glucocorticoid receptor beta. *Mol Cell Biol* 2003; 23: 4319-30.
77. KOZACI DL, CHERNAJOVSKY Y, CHIKANZA IC: The differential expression of corticosteroid receptor isoforms in corticosteroid-resistant and -sensitive patients with rheumatoid arthritis. *Rheumatology* (Oxford) 2007; 46: 579-85.
78. PRETORIUS E, WALLNER B, MARX J: Cortisol resistance in conditions such as asthma and the involvement of 11beta-HSD-2: a hypothesis. *Horm Metab Res* 2006; 38: 368-76.
79. LEE CK, LEE EY, CHO YS, MOON KA, YOO B, MOON HB: Increased expression of glucocorticoid receptor beta messenger RNA in patients with ankylosing spondylitis. *Korean J Intern Med* 2005; 20: 146-51.