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
Glucocorticoid therapy in RA and AS / C.M. Spies et al.

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, GCs, molecules bind to ubiquitously expressed cytosolic GC receptors (cGCRs). The activated GC/cGCR-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).

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

<table>
<thead>
<tr>
<th>Monocytes/macrophages</th>
<th>number of circulating cells ↓ (myelopoiesis ↓, release ↓)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>expression of MHC class II molecules and Fc receptors ↓</td>
</tr>
<tr>
<td></td>
<td>synthesis of pro-inflammatory cytokines (e.g. IL-2, IL-6, TNF-α) and prostaglandins ↓</td>
</tr>
<tr>
<td>T cells</td>
<td>number of circulating cells (redistribution effects ↓)</td>
</tr>
<tr>
<td></td>
<td>production and action of IL-2 ↓ (most important)</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>number of eosinophil and basophil granulocytes ↓</td>
</tr>
<tr>
<td></td>
<td>number of circulating neutrophils ↑</td>
</tr>
<tr>
<td>Endothelial cells</td>
<td>vessel permeability ↓</td>
</tr>
<tr>
<td></td>
<td>expression of adhesion molecules ↓</td>
</tr>
<tr>
<td></td>
<td>production of IL-1 and prostaglandins ↓</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>proliferation ↓</td>
</tr>
<tr>
<td></td>
<td>production of fibronectin and prostaglandins ↓</td>
</tr>
</tbody>
</table>
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 multi-protein 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 effects, 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 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.

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

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Clinical application</th>
<th>Genomic actions [receptor saturation]</th>
<th>Unspecific non-genomic actions</th>
<th>eGCR-mediated non-genomic actions</th>
<th>Clinical experience in RA</th>
<th>Clinical experience in AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium dose [&gt;7.5 - ≤30]</td>
<td>Initial therapy</td>
<td>++ [&gt;50 - &lt;100%]</td>
<td>(+)</td>
<td>(+)</td>
<td>Good response (in first 6 months)</td>
<td>No response (?)</td>
</tr>
<tr>
<td>Pulse therapy [≥250 mg for one or a few days]</td>
<td>Severe exacerbations</td>
<td>+++ [100%]</td>
<td>+++</td>
<td>(++?)</td>
<td>Good response</td>
<td>No effect on erosion progression</td>
</tr>
<tr>
<td>Intraarticular therapy</td>
<td>Acute or refractory synovitis</td>
<td>+++ [100%]</td>
<td>+++</td>
<td>(++?)</td>
<td>Good response</td>
<td></td>
</tr>
</tbody>
</table>

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Table III. Potential mechanisms mediating GC resistance.

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

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 sci-
ence and clinical research).

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acquired from these patients achieving 100% positive and 100% negative pre-
dictive 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 insen-
sitivity to GCs (63). Acquired muta-
tions in the GCR gene due to therapy or
selection have been observed in hema-
tological diseases (64). For rheumatic
diseases, genome analysis up to now
has failed to show any GCR gene alter-
ations. Several different mechanisms
may mediate this phenomenon. Poten-
tial mechanisms for GC resistance are
summarised in Table III.

It is somewhat surprising that only very
few data are available on the phenom-
emon 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 en-
hanced when compared with that of RA
and controls (79). The level of cGCR
beta mRNA expression was apparently
not related to the inflammatory mark-
ers or disease activity scores in RA and
AS patients, a finding which suggests that
it is not induced by the inflamma-
tory reaction. To our knowledge, no
other specific investigations have been
carried out in this regard.


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