Novel glucocorticoids: where are we now and where do we want to go?

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Received and accepted on August 28, 2015.

Clin Exp Rheumatol 2015; 33 (Suppl. 92): S29-S33.

Key words: glucocorticoid therapy, benefit:risk ratio, modified-release prednisone, liposomal glucocorticoids, selective glucocorticoid receptor agonists.

Competing interests:
F. Buttgereit has received consultancy fees, honoraria and travel expenses from Merck Serono, Horizon Pharma (formerly Nitec Pharma) and Mundipharma Int. Ltd., and grant support from Merck Serono and Horizon Pharma.
J.W.J. Bijlsma has received consultancy fees from Horizon Pharma (formerly Nitec Pharma) and Mundipharma Int.
C.M. Spies has declared no competing interests.

ABSTRACT

Glucocorticoid (GC) therapy is widely accepted as effective treatment for many inflammatory conditions. However, the potential of GC to produce adverse effects may prompt both patients and prescribing doctors to take a critical view on these important drugs. The increasing awareness of potential side effects suggests that the improvement of the benefit:risk ratio represents both a current need and an ongoing challenge. The developing and detailed knowledge on mechanisms of GC action has resulted in exploration of numerous approaches to optimise treatments with these important drugs. Most advanced is a chronotherapeutic formulation of prednisone (termed modified- or delayed-release prednisone) that has been recently approved in many European and other countries, and very recently also in the United States. Another interesting example is the development of selective GC receptor (GR) agonists, with clinical studies being currently underway. The development of so called liposomal GC is ongoing. However, another approach, the synergistic combination of prednisolone and dipyridamole, has been recently discontinued because a phase 2b study with the treatment in patients with rheumatoid arthritis showed a statistically significant improvement in disease activity score measured in 28 joints (DAS28) compared with placebo, but not compared with prednisolone alone. Other interesting developments and promising concepts include the development of nitrosteroids, targeting the membrane-bound GR and the use of extracts of the medicinal plant Tripterygium wilfordii Hook F.

With over 60 years of experience with glucocorticoids (GC), the number of patients treated and the range of clinical applications is extensive, and GC are still widely used in clinical medicine today. For example, they form a mainstay of therapy for rheumatoid arthritis (RA) since they are cost-effective drugs that exert strong anti-inflammatory, immunosuppressive and disease-modifying therapeutic effects. In recent phase II–V trials investigating biological drugs in RA, 39–70% of patients were concomitantly treated with GC (1).

GC therapy is widely accepted as effective treatment for many inflammatory conditions. However, the potential of GC to produce adverse effects may prompt both patients and prescribing doctors to take a critical view on these important drugs. As with all diagnostic and therapeutic approaches in medicine, the primary aim is a positive benefit: risk ratio when using these important drugs. In clinical medicine, this means that it is clearly wrong not to treat conditions, such as an active giant cell arteritis or a flare of systemic lupus erythematosus (SLE), which clearly benefit from this drug. On the other hand, it is equally wrong to make use of GC when not indicated or to use them at doses that are higher than required or for longer duration than necessary (Fig. 1). Consequently, this increasing awareness of the potential adverse effects suggests that the improvement of GC benefit:risk ratio represents both a current need and an ongoing challenge. The developing and detailed knowledge of mechanisms of GC action (2, 3), has resulted in exploration of numerous approaches to optimise treatments with these important drugs (4). All these approaches ultimately aim to answer one underlying salient question: How can we optimise treatments with GC?

It is important to establish the sensible approaches in order to reach this aim (*i.e.* the grey area in Fig. 1). There are essentially three viable approaches currently available:

1. Improvement of current guidelines and recommendations on optimal use of these drugs based on existing

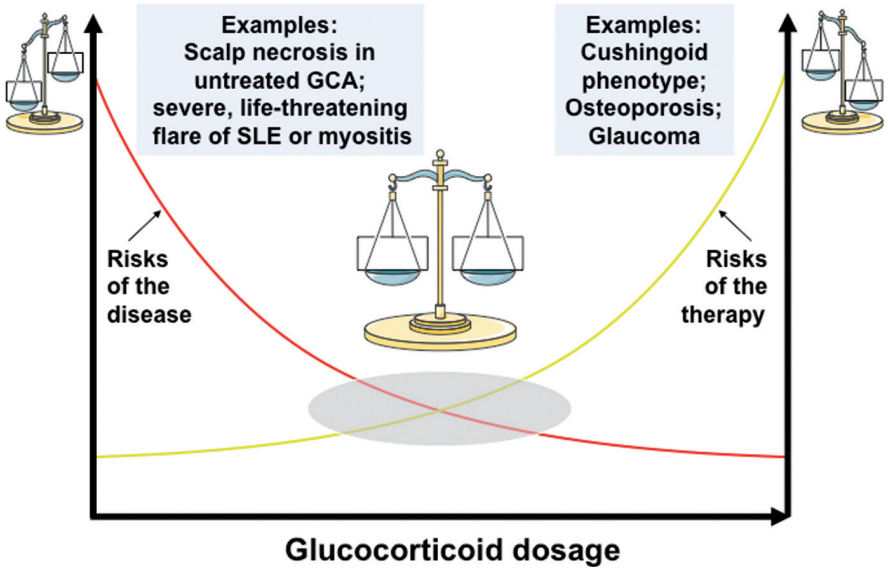

Fig. 1. Glucocorticoid therapy in rheumatology: a balance of risks.
GCA: giant cell arteritis; SLE: systemic lupus erythematosus; Grey area: optimal use of glucocorticoids.

knowledge. Examples in the field of rheumatology are given in Table I.

2. Clinical trials conducted to determine optimal use of GC treatment (such as in combination with disease-modifying anti-rheumatic drugs). This is discussed separately in the joint article to this one (12).
3. Development of novel, improved GC drugs.

This article summarises the current status for approach (3): the development of novel, improved GC drugs (Fig. 2).

Modified- or delayed-release prednisone (MR/DR prednisone)

The most advanced development of novel, improved GC drugs is a chronotherapeutic prednisone formulation that is referred to as modified-release prednisone (MR prednisone) in Europe and delayed-release prednisone (DR prednisone) in the United States. The CAPRA-1 (Circadian Administration of Prednisone in Rheumatoid Arthritis) study of 288 patients with active RA investigated the efficacy and safety of MR/DR prednisone. In this study, half of the patients were randomly allocated MR/DR prednisone tablet and half continued to receive their usual dose of standard prednisone tablet during an initial 3-month double-blind phase, followed by a 9-month open-label extension during which all patients received the chronotherapeutic formulation (13). The new formulation was shown to be clinically superior to the conventional immediate-release preparation with respect to reduced morning joint stiffness and clinical control of the disease. Levels of the pro-inflammatory cytokine, interleukin 6 (IL-6), were also reduced following MR/DR prednisone treatment but remained unchanged with standard prednisone treatment. The safety profile showed no differences between the two formulations.

At the end of the open label phase of treatment with MR/DR prednisone, the duration of morning stiffness was approximately half that seen at baseline, and 37% of patients achieved improvement according to the American College of Rheumatologists (ACR) 20 criteria (14).

The CAPRA-2 study provided further information on safety and efficacy [15]. This 12-week, double-blind, placebo-controlled study included patients with active RA (n = 350) despite treatment with disease-modifying antirheumatic drug (DMARD) therapy. Patients were randomised 2:1 to supplemental treatment with MR/DR prednisone 5 mg or placebo once daily in the evening. The addition of MR/DR prednisone to DMARD therapy resulted in higher response rates for ACR20 and ACR50, and a greater median relative reduction from baseline in morning stiffness at week 12 than the addition of placebo.

Table I. Some recommendations on the use of GCs in rheumatology published over the last 12 years.

Aspects of GC treatment	Publication year	Reference
Standardised nomenclature for GC dosages and treatment regimens	2002	Buttgereit *et al.* Ann Rheum Dis (5)
Safety of low dose GC treatment in rheumatoid arthritis	2006	Da Silva *et al.* Ann Rheum Dis (6)
European League Against Rheumatism (EULAR) evidence-based recommendations on the management of systemic GC therapy in rheumatic diseases	2007	Hoes *et al.* Ann Rheum Dis (7)
Improving the implementation of the EULAR recommendations on the management of systemic GC therapy in rheumatic diseases	2010	van der Goes *et al.* Ann Rheum Dis (8)
Systematic literature review informing the EULAR recommendations for the management of RA	2010	Gorter *et al.* Ann Rheum Dis (9)
Monitoring adverse events of low-dose GC therapy: EULAR recommendations for clinical trials and daily clinical practice	2010	van der Goes *et al.* Ann Rheum Dis (10)
EULAR evidence-based recommendations on the management of medium to high dose GC therapy in rheumatic diseases	2013	Duru *et al.* Ann Rheum Dis (11)

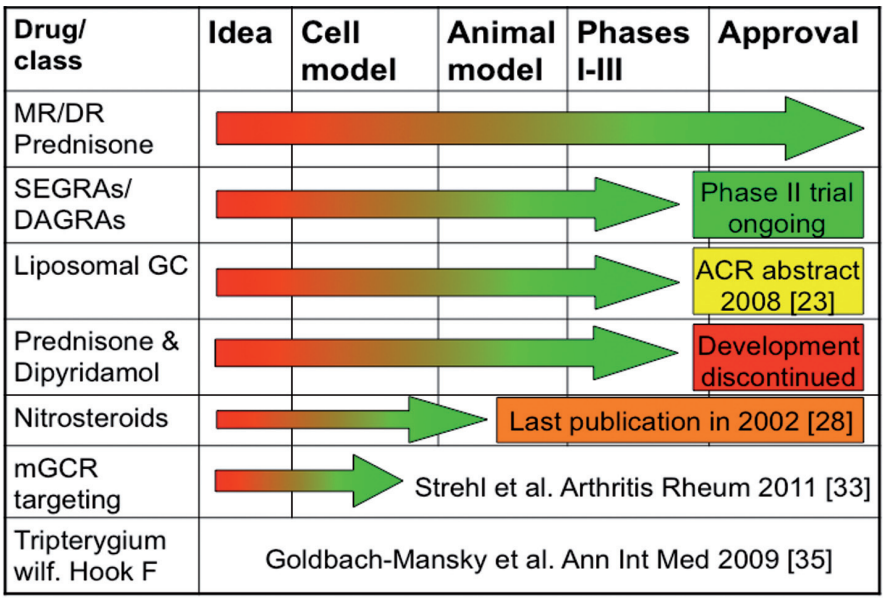

Fig. 2. Overview of the pipeline of novel glucocorticoids and glucocorticoid receptor ligands. GC: glucocorticoid; MR/DR: modified-release/delayed-release; mGCR: membrane GC receptor; SEGRA/DAGR: selective GC receptor agonists/dissociated agonists of the GC receptor.

Patients receiving MR/DR prednisone also demonstrated significantly greater reduction in severity of RA and fatigue, as well as greater improvement in physical function at week 12 than those receiving placebo. The incidence of adverse events was similar in the treatment arms. MR/DR prednisone has been approved in 16 European countries as well as in Australia, New Zealand, Israel and Korea (trade name: Lodotra) and recently (July 2012) also in the United States (trade name: RAYOS) to treat rheumatologic (and other) conditions (Fig. 2).

GR ligands

Interesting and recent approaches to optimise GC treatment include the development of innovative GR ligands. One example is the development of selective GR agonists (SEGRAs). These drugs may also be called dissociated agonists of the GC receptor (DAGRs). The rationale for this approach is based on the suggestion that some GC actions (so called transrepression effects) are to a greater extent responsible for desirable anti-inflammatory and immunomodulating effects than other actions (so called transactivation effects) that are associated with frequently occurring side effects. The idea of developing SEGRAs is, therefore, to use transrepression-mediated GC effects almost exclusively thereby inducing potent GC therapeutic activity with reduced side effects (16). This concept, however, has been challenged by recent experimental findings, including the observation that key anti-inflammatory actions of GC are caused by activating genes such as IκB, MKP-1 (a crucial anti-inflammatory gene) and IL-10 (a potent immunomodulatory and anti-inflammatory cytokine) and GC-induced leucine zipper (GILZ), a protein which inhibits the function of NFκB and AP-1 (17-19). Summarising and interpreting these data, Vandevyver *et al*. wrote in a very recent review: "Many recent reports undermine this dogma by clearly showing that GR dimer-dependent transactivation is essential in the anti-inflammatory activities of GR. Many of these studies used GR(dim/dim) mutant mice, which show reduced GR dimerisation and hence cannot control inflammation in several disease models" (20).

Furthermore, convincing data are still missing to demonstrate clinical efficacy and safety in with SEGRAs in rheumatic diseases, though clinical studies are currently underway. One key example is an ongoing phase 2, randomised, double blind assessment of efficacy and safety of the experimental GC compound PF-04171327 (1, 5, 10, 15 mg dose, daily) compared to 5 mg and 10 mg prednisone daily and placebo daily in subjects with RA (with background treatment of methotrexate) over an 8 week period followed by 4 week period of tapering of study drug. The estimated completion date is December 2013 according to the information given under http://clinicaltrials.gov/show/NCT01393639 (Fig. 2).

Liposomal GC

Another example of an interesting approach to improve the therapeutic benefit of conventional GC is the targeted delivery of GC using liposomal formulations. The concept here is that liposomes filled with glucocorticoid molecules have been shown to allow persistent therapeutic effects of targeted high GC concentration with separation of benefits/risks. For example, liposomes with dexamethasone molecules inside were effective in animal models such as collagen-induced arthritis (CIA) and antigen-induced arthritis (AIA) with no impact on hypothalamic-pituitary-adrenal (HPA) axis and blood glucose (compared to significant effects with free dexamethasone) (21, 22). As another example, long-circulating pegylated (PEG) liposomes have been shown to be well tolerated and effective in a phase 1, 12-week study of 16 patients with RA where a single liposome injection (150mg *i.v.*) resulted in a faster and more pronounced decrease in DAS and in a better improvement of ACR criteria (compared with 120 mg methylprednisolone *i.m.*). It should be noted, however, that the results of this study were only presented in form of an abstract/poster at the ACR meeting in 2008 (Fig. 2), but not so far reported in a full-length peer-reviewed paper (23). More information in this regard can be obtained from other publications (24, 25), and from a recent review published in 2011 by van den Howen *et al*. (26).

The prednisone and dipyridamol combination drug

It was hypothesised that treatment with conventional GC already available to clinicians may be improved through synergistic multi-target action of a

combination drug. The combination of prednisolone and the antithrombotic drug, dipyridamole, was shown to suppress synergistically the release of pro-inflammatory cytokines and to produce anti-inflammatory activity in acute and chronic disease models using only a sub-therapeutic dose of prednisolone (27). The exact molecular mechanism underlying this synergistic multi-target action of these two drugs was not clear. Nevertheless, a 12-week, five-arm, double-blind, placebo-controlled phase 2b study was performed in which 259 RA patients on stable DMARD therapy with moderate to severe disease were treated with the combination drug (named Synavive) or placebo, 5mg/d prednisone 5 mg/day or the individual components (*i.e.* prednisolone 2.7 mg/day or dipyridamole 360 mg/day). The combination drug achieved a statistically significant improvement in DAS28 compared to placebo (17% vs. 10%), but not compared to prednisolone 2.7 mg/day alone (http://phx.corporate-ir.net/phoenix.zhtml?c=148036&p=irolnewsArticle&ID=1733297&highlight). For this reason, the company investigating the combination drug (Zalicus) stated that "In the absence of a clinically meaningful benefit with Synavive compared to its active GC component, Zalicus will discontinue further clinical development with Synavive." (Fig. 2)

Other developments

There are other interesting developments in the field (Fig. 2).

Nitrosteroids

Nitrosteroids release low levels of nitric oxide (NO). The prototype 21-NO-prednisolone (or NCX-1015) has been shown to be endowed with enhanced anti-inflammatory properties and reduced side effects compared with conventional prednisolone. Specifically, this drug was shown (i) to be more potent than prednisolone in models of acute and chronic inflammation including CIA but (ii) not to activate primary osteoclast activity in an *in vitro* assay of bone resorption (unlike prednisolone) (28). Unfortunately, this promising report has not yet been followed by more information or new data.

Targeting the membrane-bound GR

Membrane bound receptors for GC (mGR) exist on human immune cells in small numbers (29) and can be identified by high-sensitivity immunofluorescence (30). These receptors are up-regulated in monocytes following vaccination as well as in monocytes and B cells of patients with ankylosing spondylitis (31), and down-regulated by GC in patients with SLE (32). In a recent paper, it was shown that (i) the human GR gene encodes for both cytosolic GR (cGR) and mGR (as shown by exonwise knockdown of GR via RNAi Technology) and that (ii) the mGR retains functional activity, as indicated by induced phosphorylation of p38 MAPK due to DEX-BSA treatment (33). From these data it is concluded that specifically targeting the mGCR could be of therapeutic benefit under certain circumstances, and therefore, more work is currently being done in order to test this hypothesis.

Tripterygium wilfordii Hook F (TwHF)

Extracts of the medicinal plant *Tripterygium wilfordii Hook F (TwHF)* have been used in China for centuries to treat inflammatory diseases. The major active components of the TwHF extract, triptolide and tripdiolide, have been proposed to bind to the glucocorticoid receptor (34). Extract-GR complex, unlike the glucocorticoid (*e.g.* dexamethasone)-GR complex, does not activate the genes containing glucocorticoid response elements, but is possibly effective in inhibiting the activation of nuclear proinflammatory transcription factors, such as NF-κB (34). A clinical study has investigated the effects of TwHF extract, 60 mg 3 times daily, or sulfasalazine (SSA), 1 g twice daily in 121 patients with active RA and 6 or more painful and swollen joints. Patients could continue stable doses of oral prednisone or non-steroidal anti-inflammatory drugs (NSAIDs) but had to stop taking DMARDs at least 28 days before randomisation. Significantly more patients who continued treatment for 24 weeks and used stable oral prednisone and NSAIDs attained ACR 20 response criteria with TwHF extract than with SSA (35).

In summary, GC are still among the most frequently used and most important drugs to treat inflammatory and autoimmune diseases or conditions. However, their potential to produce sometimes severe adverse effects (especially if given at high dosages for a long time) limits their use. There is, however, an increasing awareness of this problem, and as a consequence, some interesting new approaches to improve the benefit:risk ratio of this important class of drugs have already proved successful. Other interesting projects are currently planned or already underway.

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