A Fresh Look at Glucocorticoids
How to Use an Old Ally More Effectively

Frank Buttgereit, M.D.

Abstract

Glucocorticoids form a mainstay of therapy for rheumatoid arthritis (RA) and other conditions since they exert strong anti-inflammatory, immunosuppressive, and disease-modifying therapeutic effects. However, there is increasing awareness of the potential for these drugs to produce adverse effects. Therefore, improvement of the glucocorticoid benefit-risk ratio represents both a current need and an ongoing challenge. The development of recommendations to implement a more effective and safer use of these important drugs is one useful path to pursue. An additional avenue is the development of innovative glucocorticoids or glucocorticoid receptor ligands. Also, treatment with conventional glucocorticoid preparations currently available to clinicians may be improved. The most advanced development in the latter regard is a novel chronotherapeutic prednisone formulation called delayed-release (DR) or modified-release prednisone. The CAPRA (Circadian Administration of Prednisone in Rheumatoid Arthritis) studies confirmed that optimizing the timing of GC administration improves the benefit-risk ratio of long-term low dose glucocorticoid treatment in patients with rheumatoid arthritis. DR prednisone has been approved in 16 European countries as well as Australia and Israel. Very recently, DR prednisone was also approved in the United States to treat rheumatologic conditions such as RA, polymyalgia rheumatica and psoriatic arthritis, as well as respiratory conditions such as COPD and asthma.

With over 60 years of experience with glucocorticoids (GC), the number of patients treated and the range of clinical applications is more extensive than with other treatments. The diversity of clinical use across many therapeutic domains is indicated in Table 1. This article, however, focuses more specifically on the use of GC in rheumatic diseases.

GCs are widely used in rheumatic diseases because they are among the most effective (and cost-effective) anti-inflammatory and immunomodulatory drugs currently available. As such, GCs form a mainstay of therapy for rheumatoid arthritis (RA). This is illustrated by the finding that usually more than 50% of RA patients included in phase II–IV trials investigating biological drugs are concomitantly treated with GC. Similar use of GCs occurs outside of clinical trials, in routine “real-world” practice. For example, Neovius and coworkers reported that 28,698 of 58,102 patients (49%) in a Swedish database of RA and disease-modifying drugs received GC treatment. In Germany, the proportion of GC-treated RA patients appears to be fairly constant at approximately 56%, though in recent years there has been an increase in use of GC dosages $\leq 7.5$ mg prednisone equivalent per day. However, when used incorrectly, GC have a high potential for frequent and serious side-effects. Both the wanted and the adverse effects of GC are mediated by genomic and non-genomic mechanisms of action.

Recent Approaches to Optimize Treatments with Glucocorticoids

The increasing awareness of the potential for GCs to produce adverse effects and the increasingly detailed knowledge on their mechanism of action has initiated a variety of approaches to optimize treatments with these important drugs. Several of these approaches are outlined in Table 2.

An early approach in this regard was observed in the 1950s and 1960s, when new therapeutic GC drugs were
synthesized. These drugs (e.g., prednisone/prednisolone, methylprednisolone) differed from physiological cortisone by exhibiting reduced mineralocorticoid activity but significantly increased GC potencies. In the following years, the advantages of local administration (e.g., intra-articular GC injections, GC eye drops, inhaled GC, GC enema) in certain diseases became apparent.

Guidelines and recommendations have been developed to improve the benefit-risk ratio of these drugs. Examples are the recently published recommendations on monitoring of adverse events of GC treatment in RA.8 Additionally, EULAR has published evidence-based recommendations on the management of systemic GC therapy in rheumatic diseases.9

Further interesting and recent approaches to optimize GC treatment include the development of innovative GCs or GC receptor ligands. One example is the development of selective GR agonists (SEGRAs). This approach is based on the suggestion that some GC actions (the so called transrepression effects) are to a greater extent responsible for desirable anti-inflammatory and immunomodulating effects than the other actions (the so called transactivation effects) that are associated with frequently occurring side effects (but also with some immunosuppressive activities). 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. This concept, however, has recently been challenged by experimental observations, and convincing data are still missing to demonstrate clinical efficacy and safety.10

Table 1  Examples of the Clinical Use of Glucocorticoids

<table>
<thead>
<tr>
<th>Pulmonology</th>
<th>asthma, sarcoidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatology</td>
<td>rheumatoid arthritis, systemic lupus erythematosus, myositis, gout</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>ulcerative colitis, Crohn’s disease</td>
</tr>
<tr>
<td>Immunology</td>
<td>allergic diseases</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>replacement therapy in glucocorticoid deficiency</td>
</tr>
<tr>
<td>Nephrology</td>
<td>glomerulonephritis</td>
</tr>
<tr>
<td>Oncology</td>
<td>lymphoproliferative disorders</td>
</tr>
<tr>
<td>Dermatology</td>
<td>connective tissue and immunobullous diseases, vasculitis, dermatitis</td>
</tr>
<tr>
<td>Neurology</td>
<td>multiple sclerosis, myasthenia gravis</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>uveitis, iritis, scleritis</td>
</tr>
</tbody>
</table>

Table 2  Approaches to Optimizing Treatments with Glucocorticoids20

| Synthesize GCs with decreased mineralocorticoid but increased anti-inflammatory activity |
| e.g., prednisone/prednisolone |
| Deliver GCs directly to the site of inflammation |
| e.g., intra-articular injections |
| Optimize dosing regimens (‘give as much as necessary, but as little as possible’)
| e.g., development of recommendations and guidelines |
| Develop of innovative GCs or GC receptor ligands |
| e.g., SEGRAs, nitrosteroids |
| Improve treatment with conventional GCs |
| e.g., targeted delivery with a specific formulation to change the timing, prednisone/dipyridamole combination drug, liposomal GCs |

Clinicians may also be improved, for example, by selectively amplifying the GC anti-inflammatory activity through synergistic multi-target action of a combination drug.11 The combination of prednisolone and the antithrombotic drug, dipyridamole, has been 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. The exact molecular mechanism underlying this synergistic multi-target action of these two drugs is, however, not clear at the moment.10,11 Another example of an interesting approach to improve the therapeutic benefit of conventional GC is the targeted delivery of GC using liposomal formulations.12 Additional work is needed to gauge the ultimate clinical utility of these interesting drug development concepts.

Further advanced, however, is a chronotherapeutic prednisone formulation that is referred to in the United States as “delayed-release prednisone” (DR prednisone) and in Europe as “modified-release prednisone” (MR prednisone); these are interchangeable terms that refer to the same drug. For clarity, we will use in this review the term “DR prednisone.”

**Chronotherapeutics: Pathophysiologic Rationale in RA**

It has long been known that many body functions and processes are driven by internal clocks. As a result, ultradian, circadian, and other body rhythms are important under physiological and pathophysiological conditions. Accordingly, the treatment of diseases may be more or less successful depending on the time that a medicine is taken. Coordinat-
ing biological rhythms (chronobiology) with medical (drug) treatment is called chronopharmacotherapy and represents a new take on the term “targeted therapy.”

Chronobiology plays a prominent role in patients with RA. These patients typically show circadian patterns of pain, stiffness, and functional disability, as well as cyclic variations in hormone levels and cytokine concentrations. Major symptoms, such as pain, inflammation, and stiffness, are usually most severe in the morning hours. These symptoms are thought to be caused by elevated nocturnal levels of interleukin-6 (IL-6), tumor necrosis factor (TNF), and other pro-inflammatory cytokines. Of central importance is IL-6, which is the most abundant cytokine in the serum and synovial fluid of patients with RA and is thought to mediate both systemic (acute-phase response, anemia, thrombocytosis, fatigue, osteoporosis) and articular symptoms. Levels of IL-6 and its soluble receptor in synovial fluid show significant correlation with measures of chronic synovitis and the severity of joint destruction in patients with RA. IL-6 also facilitates the recruitment and activity of neutrophils, monocytes, endothelial, and bone-derived cells. In addition, IL-6 has an important role in the pathophysiology of arthritic pain.

**Glucocorticoid Chronotherapy with Delayed-Release Prednisone**

If the nocturnal rise in IL-6 and other pro-inflammatory cytokines initiates a cascade of events promoting morning symptoms of pain, fatigue, stiffness and immobility, it was postulated that preventing this rise could be more effective than treating established symptoms. IL-6 and other humoral factors and cellular reactions involved in RA pathogenesis can be targeted with GC. However, GC is usually administered between 6 a.m. and 8 a.m., which may not be optimal since peak serum drug concentration occurs well after the circadian rise in inflammatory cytokines. It was hypothesized that improving the timing of GC administration may help to optimize RA therapy. Arvidson and associates confirmed this hypothesis by demonstrating that night-time administration (2 a.m.) of GC was more effective at reducing symptoms in RA patients than administration at the usual time (7:30 a.m.). However, waking the patient each night to administer a standard GC drug prior to the flare-up of cytokine synthesis and inflammatory activity is clearly not a feasible or practical administration option. Thus, the DR prednisone tablet was developed.

DR prednisone is a tablet-in-tablet formulation, consisting of an immediate-release prednisone core tablet, surrounded by an inactive outer tablet shell. This formulation is designed to release prednisone about 4 hours after ingestion, i.e., at approximately 2 a.m. if taken at bedtime. Gastric and intestinal fluid slowly penetrates into the tablet shell independent of the gastrointestinal pH and eventually triggers release of the active drug. Once released, the pharmacokinetic and pharmacodynamics profile of prednisone is comparable to conventional immediate release prednisone. DR prednisone is available in strengths of 1, 2, and 5 mg, which are distinguished from one another by both color and debossing.

The efficacy and safety of DR prednisone were investigated in the CAPRA-1 (Circadian Administration of Prednisone in Rheumatoid Arthritis) study of 288 patients with active RA, half of whom were randomly allocated DR prednisone tablet and half standard prednisone tablet during an initial 3-month double-blind phase, followed by a 9-month open-label extension. The new formulation was shown to be clinically superior to the conventional immediate-release preparation with respect to reducing morning joint stiffness and clinical control of the disease. Levels of IL-6 were also decreased by DR prednisone but remained unchanged with IR prednisone. The safety profile showed no differences between the two preparations.

During the open-label extension period, all patients were treated with DR prednisone. After 12 months of treatment (i.e., at the end of the open label phase), the duration of morning stiffness was reduced from baseline by about 50%, and 37% of patients achieved improvement according to the ACR20 criteria. Corticotropic-releasing hormone (CRH) tests were performed in a subgroup of patients. No differences were seen between DR prednisone and standard prednisone with regard to the influence on hypothalamic-pituitary-adrenal axis.

Further, safety and efficacy data were obtained from the CAPRA-2 study. In this 12-week, double-blind, placebo-controlled study, patients with active RA (N = 350) were randomized 2:1 to receive DR prednisone 5 mg or placebo once daily in the evening in addition to their existing RA DMARD therapy. DR prednisone plus DMARD therapy resulted in higher response rates for ACR20 (48% vs. 29%, p < 0.001) and ACR50 (22% vs. 10%, p = 0.006), and a greater median relative reduction from baseline in morning stiffness (55% vs 35%, p < 0.002) at week 12 compared with placebo plus DMARD therapy. Significantly greater reductions in severity of RA (Disease Activity Score 28) (p < 0.001) and fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue score) (p = 0.003), as well as a greater improvement in physical function (36-item Short-Form Health Survey score) (p < 0.001), were seen at week 12 with DR prednisone compared with placebo. The incidence of adverse events was similar for DR prednisone (43%) and placebo (49%).

These studies confirm that optimizing the timing of GC administration improves the benefit-risk ratio of long-term low-dose GC treatment in patients with RA. DR prednisone has been approved in 12 European countries in 2009 (trade name: Lodotra) and very recently in the United States (trade name: RAYOS, FDA approval on July 26, 2012). Although the European approval is restricted to RA, United States labeling includes a considerable number of indications based on the FDA 505(b)(2) regulatory pathway. This pathway
was supported by bridging pharmacokinetics to immediate release prednisone and clinical studies conducted with DR prednisone. The approved indications in the United States include rheumatologic conditions, such as polymyalgia rheumatica, and psoriatic arthritis, as well as respiratory conditions, such as chronic obstructive pulmonary disease (COPD) and asthma, which also appear to be mediated—at least in part—by inflammatory chronobiology.

Summary
In conclusion, GCs are among the mainstays of treatment for RA and other inflammatory diseases since they exert strong anti-inflammatory, immunosuppressive, and disease-modifying therapeutic effects. However, the improvement of their benefit-risk ratio represents both a current need and an ongoing challenge. The development of recommendations to implement a more effective and safer use of these important drugs is one useful way to go. An additional avenue is the development of improved GC formulations. The most advanced is DR prednisone. This GC drug represents a novel chronotherapeutic approach and has been recently approved in the United States to treat rheumatologic conditions, such as RA, polymyalgia rheumatica, and psoriatic arthritis, as well as respiratory conditions, such as COPD and asthma.

Disclosure Statement
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References