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INVITED REVIEW

Therapeutic mechanisms of glucocorticoids, their administration and chronotherapy

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This manuscript was peer-reviewed by Dr. Melih Babaoğlu

ABSTRACT

Glucocorticoids represent a cornerstone in the treatment of inflammatory and autoimmune diseases due to their potent anti-inflammatory and immunosuppressive effects. These steroid hormones, including endogenous cortisol and synthetic analogs like prednisone and dexamethasone, exert their effects through genomic and non-genomic pathways, targeting key inflammatory mediators. While genomic mechanisms regulate long-term gene expression, non-genomic pathways enable rapid modulation of immune responses, particularly at high doses. Despite their therapeutic efficacy, glucocorticoid use is often limited by significant adverse effects, including osteoporosis and metabolic disorders. Chronotherapy, which aligns medication timing with circadian rhythms, enhances therapeutic outcomes while reducing side effects, particularly in diseases like rheumatoid arthritis where inflammation peaks in the early morning. Emerging innovations, such as selective glucocorticoid receptor agonists (SEGRAs) and liposomal drug delivery systems, offer targeted anti-inflammatory effects with reduced systemic toxicity. These advancements highlight the potential for optimizing glucocorticoid therapy to achieve maximum efficacy while mitigating adverse effects. This review underscores the importance of understanding glucocorticoid mechanisms, administration methods, and novel therapeutic strategies to improve outcomes in inflammatory and autoimmune diseases.

Keywords: glucocorticoid mechanisms, chronotherapy, glucocorticoid resistance.

Introduction and Terminology

Glucocorticoids are a pivotal class of steroid hormones extensively utilized in managing inflammation, immune responses, and various metabolic processes [1,2]. Cortisol is the primary endogenous glucocorticoid in humans, known therapeutically as hydrocortisone. It is essential for life, secreted in a circadian rhythm, with physiological secretion ranging from 10-20 mg per day [3]. Approximately 10% of circulating cortisol is free, while the remainder is bound to corticosteroid-binding globulin (transcortin) and after CBG saturation, about 80% binds to albumin. The level of free cortisol varies between 1-100 nanomole/L, depending on the diurnal rhythm [4]. Plasma cortisol concentrations typically measure around 16 mcg/dL in the morning and 4 mcg/dL in the evening, with a half-life of 60-90 minutes, metabolized in the liver and excreted by the kidneys [5]. Blood cortisol levels are influenced by many factors besides the diurnal rhythm; in the presence of estrogen, CBG concentrations increase, potentially altering cortisol levels. Also, in cases of very low serum albumin levels, it may be necessary to reduce the steroid dose, although there is no specific research in rheumatology regarding this adjustment

Synthetic glucocorticoids have been structurally modified to enhance their binding affinity to glucocorticoid receptors (GRs) (Figure 1) [1,6]. Their

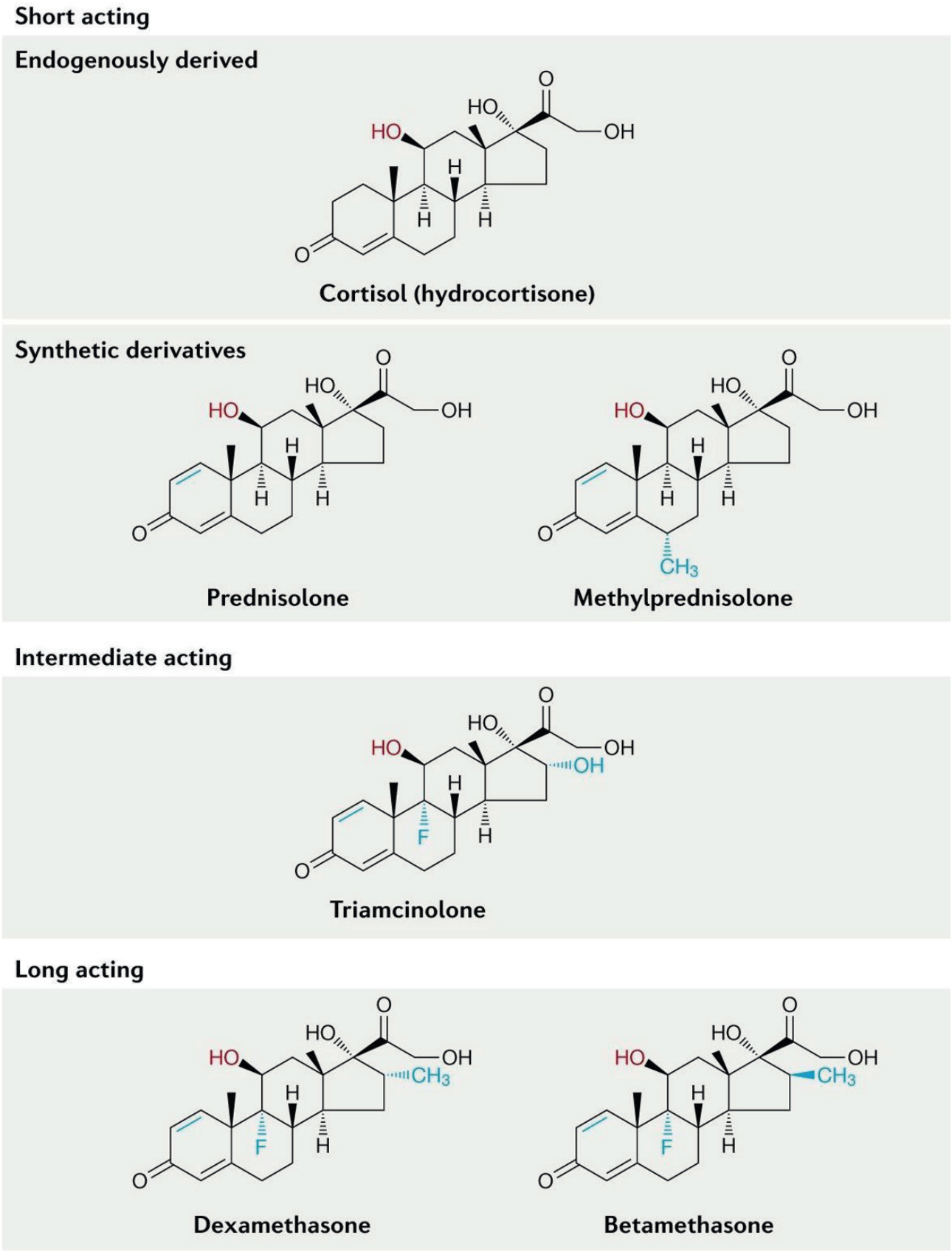

Figure 1. Chemical structures of glucocorticoids based on duration of action, [10] Blue indicates differences, red indicates similarities.

potent anti-inflammatory and immunosuppressive effects make them indispensable in treating a wide range of conditions, including autoimmune diseases like vasculitis [7]. Overall, they have been used in 1% of general population, and more in elderly as 3% [8].

Despite their effectiveness, the use of glucocorticoids in chronic rheumatic diseases, particularly rheumatoid arthritis (RA), appears to be decreasing. This decline is largely driven by the advent of biologic therapies, which offer more targeted immune modulation with fewer systemic side effects. However, for certain autoimmune conditions such as systemic vasculitis, systemic lupus erythematosus (SLE), and polymyalgia rheumatica, glucocorticoids remain indispensable, particularly for achieving rapid immunosuppression in acute settings. The clinical challenge lies in balancing the need for inflammation control with the long-term risks posed by glucocorticoid therapy. To maximize therapeutic efficacy and minimize adverse effects, a comprehensive understanding of their molecular mechanisms, administration methods, and the role of chronotherapy is essential [9].

Mechanisms of Action of Glucocorticoids

The effects of glucocorticoids are primarily mediated through their interaction with the glucocorticoid receptor (GR), a ligand-activated transcription factor that regulates gene expression [1,10]. Endogenous glucocorticoids, such as cortisol, can bind to both the glucocorticoid receptor (encoded by NR3C1) and the mineralocorticoid receptor (encoded by NR3C2). The glucocorticoid receptor, found in most body cells, is responsible for mediating both the anti-inflammatory effects and the adverse effects of therapeutic glucocorticoids. It contains structural domains for ligand binding, nuclear localization, and DNA interaction. When unbound, it resides in the cytoplasm but moves to the nucleus upon activation by glucocorticoids. The mineralocorticoid receptor, mainly expressed in tissues regulating salt and water balance, such as the kidneys and sweat glands, binds to glucocorticoids like cortisol but is protected from overactivation by 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2), which inactivates glucocorticoids in these tissues. These effects are exerted through both genomic and non-genomic pathways, each contributing to the overall therapeutic profile of these agents [11].

Genomic and Non-Genomic Pathways

1. Genomic Mechanisms: Glucocorticoids exert their effects largely through genomic mechanisms. Upon entering the cell, glucocorticoids bind to cytoplasmic GRs, which then translocate to the nucleus. This complex either activates or represses the transcription of target genes, suppressing inflammatory cytokines, chemokines, and enzymes integral to inflammatory processes. These genomic actions, taking several hours to manifest, underpin the long-term effects of glucocorticoids [1].

2. Non-Genomic Mechanisms: In addition to their genomic actions, glucocorticoids also exert rapid effects through non-genomic pathways. Non-genomic effects do not involve changes in gene transcription. These include interactions with membrane-bound receptors and cellular components, leading to the swift modulation of signaling pathways like MAPK and PI3K [12]. These actions can occur within minutes, providing immediate anti-inflammatory benefits. Non-genomic effects are particularly prominent at doses exceeding 100 mg/day of prednisone or its equivalent. Methylprednisolone and dexamethasone are especially responsive to non-genomic pathways, which include:

   - Direct Inhibition of Phospholipase A2: The GC-GR complex directly inhibits phospholipase A2, reducing arachidonic acid production independently of transcription.
   - Activation of Membrane-Bound GRs: Activation of membrane-bound GRs (mGRs) reduces lymphocyte activity through the p38 MAP kinase pathway.
   - Interaction with Cellular Membranes: GCs interact with immune cell membranes via chaperone proteins, leading to ATP production inhibition and decreased cell activity.

Immune Response Modulation

Glucocorticoids exert a broad and potent immunosuppressive effect by inhibiting the expression of genes that regulate cytokine production. This suppression affects both the

pre-inflammatory and inflammatory phases of immune response.Unbound receptors reside in the cytoplasm, but after binding to glucocorticoids, they are transported to the nucleus. In the nucleus, the receptor binds to the promoter region of cytokine genes, regulating their transcription and inhibiting the activation of nuclear factor kappa B (NF-κB) and AP1.These factors are crucial in initiating the expression of cytokines and other inflammatory mediators. By inhibiting the activity of NF-κB and AP1, glucocorticoids reduce inflammation at the molecular level, preventing the escalation of immune responses. This mechanism is pivotal in the treatment of autoimmune diseases like vasculitis and rheumatoid arthritis, where controlling inflammation is critical. Unlike some other immunosuppressive agents, glucocorticoids do not prevent T and B lymphocytes from recognizing antigens. Instead, they inhibit T lymphocyte differentiation and cytokine secretion (e.g., interleukins and tumor necrosis factor-alpha), thereby preventing the initiation of cellular immune responses [1,13].

The mineralocorticoid receptor (MR) is primarily found in cells involved in salt and water regulation, such as those in the distal tubule, salivary glands, sweat glands, and colonic epithelium.

Glucocorticoids have a broad immunosuppressive effect by inhibiting cytokine production, particularly affecting T and B lymphocyte function. This results in the prevention of T-cell differentiation and cytokine secretion (e.g., interleukins, TNF-α), thereby curbing cellular immune responses without compromising antigen recognition.

The action of glucocorticoids involves several critical pathways:

1. Inhibition of T-Cell Differentiation and Cytokine Secretion: Glucocorticoids prevent T cells from differentiating and secreting cytokines such as interleukin-1, -2, -3, -5, tumor necrosis factor-alpha, and interferon-gamma, thereby inhibiting the initiation of cellular immune responses. This effect is achieved through the binding of glucocorticoids to specific cytoplasmic receptors in cells, which then translocate to the nucleus to bind promoter regions of cytokine genes, inhibiting transcription and the activation of nuclear factor kappa B (NF-κB).
2. Inhibition of B-Cell Antibody Production and Induction of Apoptosis: Glucocorticoids suppress the ability of B cells to produce antibodies and increase their apoptosis.
3. Inhibition of Macrophage and Polymorphonuclear Leukocyte Function: The migration and phagocytic abilities of macrophages, their monocyte precursors, and polymorphonuclear leukocytes are inhibited, and the lysosomal stability of these cells is increased.
4. Reduction of Circulating Lymphocytes: Glucocorticoids enhance the migration of lymphocytes from the bloodstream to lymph nodes and bone marrow, reducing circulating lymphocyte levels, particularly in T cells, leading to lymphopenia and the atrophy of lymphatic tissue.
5. Inhibition of Complement System Activation: Glucocorticoids also inhibit the activation of the complement system, which contributes to immunologic inflammatory responses.

Receptor Modulation and Resistance

The therapeutic efficacy of glucocorticoids can be undermined by the development of glucocorticoid resistance, a phenomenon driven by factors such as GR down-regulation, the presence of less active GR isoforms, and the inhibitory interactions between GRs and other transcription factors. Addressing these mechanisms is crucial for optimizing glucocorticoid therapy in resistant cases [1,14].

Glucocorticoid resistance, particularly in chronic inflammatory diseases, may result also from the upregulation of the GRβ isoform, or disease-induced chromatin changes that restrict receptor binding to gene promoters. GRβ functions as a **dominant-negative inhibitor**, preventing the classic GRα isoform from effectively binding to DNA and exerting its anti-inflammatory effects. Unlike GRα, which mediates most of the therapeutic actions of glucocorticoids, GRβ does not bind glucocorticoids and can **heterodimerize** with GRα, disrupting its ability to regulate inflammatory gene transcription. Studies have shown that **upregulation of GRβ** in response to chronic inflammation may lead to reduced glucocorticoid sensitivity, further complicating treatment efforts in diseases like vasculitis.

Administration Methods of Glucocorticoids

In clinical practice, glucocorticoids are employed as first-line agents at high doses to achieve rapid immunosuppression, particularly in conditions requiring urgent control of underlying immunologic and inflammatory processes [9]. The administration route and dosage of glucocorticoids are tailored to the nature of the disease, the organ system involved, and the severity of the condition [15]. Glucocorticoids exert their effects through both genomic and non-genomic mechanisms, with the dose being the determinant of which mechanism predominates. Doses between 40 mg and 100 mg increase the likelihood of side effects without significantly enhancing anti-inflammatory effects. Doses of 100 mg and above primarily affect inflammatory cells through non-genomic pathways, which forms the basis for new glucocorticoid dosing regimens.

Oral Administration

Commonly used for chronic conditions, oral glucocorticoids like prednisone and dexamethasone offer systemic absorption and convenience. Their effects are subject to pharmacokinetic factors, including bioavailability and half-life, making them suitable for long-term therapy.Orally administered synthetic steroids are rapidly absorbed, with most having a plasma half-life (t½) of 1–3 hours. The maximum biological effect is observed 2–8 hours post-administration, necessitating 2–3 doses per day in certain indications. These steroids are primarily metabolized in the liver, with a small portion excreted unchanged in the urine. Special caution is advised in patients with concurrent liver or kidney diseases, as these conditions may affect the drug's metabolism and excretion. Oral administration is commonly used for chronic conditions requiring long-term therapy [2].

Intravenous and Intramuscular Injection

For rapid systemic effects, as required in acute exacerbations of autoimmune diseases, intravenous or intramuscular glucocorticoids are preferred. These methods ensure swift bioavailability, critical in emergency settings [3].

Topical and Inhaled Administration

Targeted local therapy for conditions like asthma or dermatological issues minimizes systemic exposure and associated side effects. Inhaled and topical glucocorticoids are integral to managing localized inflammatory processes [4].

Dosing

In the context of immunosuppression, glucocorticoids like prednisone, prednisolone, and methylprednisolone are used at equivalent doses. For instance, 5 mg of prednisolone is equivalent in glucocorticoid effect to 4 mg of methylprednisolone, 6 mg of deflazacort, and 0.75 mg of dexamethasone (Table 1).

Glucocorticoid dosing can be categorized into several ranges based on their effects [15]:

- Low Dose (< 7.5 mg/day): Achieves approximately 50% saturation of cGRs.
- Medium Dose (7.5-30 mg/day): Saturation of cGRs ranges from 50% to 100%.
- High Dose (30-100 mg/day): Results in full saturation of cGRs, with transactivation becoming the dominant effect, often leading to side effects without significant additional anti-inflammatory benefits.
- Very High Dose (>100 mg/day): Activates non-genomic pathways predominantly.
- Pulse Therapy (≥250 mg/day): Administered for one or several days in acute situations.

Chronotherapy and Glucocorticoids

Chronotherapy refers to the timing of medication administration to align with the body's natural biological rhythms, which can enhance therapeutic outcomes and reduce side effects [16].

1. Circadian Rhythms: In rheumatoid arthritis, inflammation peaks during the night and early morning. Administering glucocorticoids to coincide with this peak, such as with night-time-release formulations, can better control nocturnal inflammation and alleviate morning symptoms. This approach maximizes therapeutic outcomes while minimizing the risk of side effects [17].

Table 1. Comparison of glucocorticoids: Duration, mineralocorticoid activity, and equivalent dosing

	Endogenous (Synthetic)	Duration of Action	Mineralocorticoid Activity	Equivalent Anti-inflammatory Dose
Cortisol (Hydrocortisone)	Endogenous	Short	Yes	20 mg
Prednisolone	Synthetic	Short	Yes	5 mg
Methylprednisolone	Synthetic	Short	No	4 mg
Triamcinolone	Synthetic	Intermediate	No	4 mg
Dexamethasone	Synthetic	Long	No	0.75 mg
Betamethasone	Synthetic	Long	No	0.6 mg

2. Cost-Effectiveness and Clinical Benefits: While chronotherapy may incur higher costs due to modified-release formulations, it proves cost-effective by improving symptom control and patient quality of life in cases where standard treatments fall short [18].

Chronotherapy, which involves aligning medication administration with the body's biological rhythms, holds significant promise in the management of vasculitis. In this context, timed-release glucocorticoid formulations such as Rayos® (delayed-release prednisone) offer an innovative approach. These formulations are designed to release glucocorticoids during the early morning hours when inflammation peaks in many autoimmune diseases, including vasculitis. By synchronizing drug release with the circadian rise in inflammatory cytokines, timed-release glucocorticoids can more effectively suppress constitutional symptoms, which are common in patients with vasculitis. This strategy not only enhances therapeutic efficacy but also helps to minimize adverse effects by reducing the overall dose needed to control symptoms. Early studies in rheumatoid arthritis have demonstrated improved symptom control and patient quality of life, suggesting that similar benefits may be achievable in vasculitis management. Different Glucocorticoid formulations are detailed at Table 2.

Despite their efficacy, glucocorticoids can induce a range of side effects, primarily due to their mineralocorticoid activity, which can lead to complications such as hypertension. To mitigate these effects, synthetic derivatives of cortisone have been chemically modified to reduce mineralocorticoid activity while enhancing glucocorticoid effects [7]. For example, fludrocortisone is a derivative with predominant mineralocorticoid properties and is not used for anti-inflammatory purposes, whereas dexamethasone and betamethasone have minimal clinically significant mineralocorticoid activity [19,20].

The placental transfer of glucocorticoids depends on the dosage, the lipophilicity of the compound, and the gestational age of the fetus. Dexamethasone, a lipophilic steroid, crosses the placenta, whereas prednisone and methylprednisolone are metabolized by the placenta, resulting in negligible fetal plasma levels when used at doses of <20 mg/day. Therefore, dexamethasone is preferred when fetal effects are desired, while prednisone derivatives (up to 20 mg) are used for maternal effects [21].

Side Effects and Management

The long-term use of high-dose glucocorticoids is associated with significant adverse effects, including metabolic effects such as weight gain, hyperglycemia, and increased risk of diabetes. In patients with rheumatoid arthritis, the risk of developing diabetes mellitus doubles with prednisolone doses of 7.5 mg or higher. This effect is primarily due to altered glucose metabolism, including decreased insulin sensitivity and increased hepatic gluconeogenesis. They can also lead to fluid retention, hypertension, and dyslipidemia.

Bone health may be compromised, leading to osteoporosis and an elevated risk of fractures. Glucocorticoids not only impair bone formation by reducing osteoblast proliferation and increasing osteoclast activity but also induce muscle wasting via the suppression of anabolic signaling pathway, shifting the balance between receptor activator of NF-κB ligand (RANKL) and osteoprotegerin (OPG) in favor of osteoclast activation. Glucocorticoids not only impair bone formation by reducing osteoblast proliferation and increasing osteoclast activity but

Table 2. Overview of glucocorticoid medications: Dosage, availability, and indications according to Food Drug Administration as of February 2023

Drug	Manufacturer	Dosage	Availability
Prednisone delayed-release (Rayos®)	Horizon	**Adults and Children:** Initial dose: 5 mg administered once daily Maintenance dose: Use the lowest dosage that will maintain clinical response depending on specific condition treated Swallow tablet whole	Tablet: 1 mg, 2 mg, and 5 mg
Prednisone (Prednisone Intensol™)	Roxane	**Adults and Children:** 5 mg to 60 mg per day, depending on specific condition treated	Oral solution: 5 mg/mL (contains 30% alcohol)
Budesonide	Generic	**Treatment of mild to moderate active Crohn's disease:** **Adults:** 9 mg once daily in the morning for up to 8 weeks; repeated 8-week courses for recurring episodes **Children (8-17 years, >25 kg):** 9 mg once daily for up to 8 weeks, followed by 6 mg once daily for 2 weeks	Enteric-coated capsule: 3 mg
Budesonide (Ortikos™)	Ferring	**Maintenance of clinical remission of mild to moderate Crohn's disease:** **Adults:** 6 mg once daily for up to 3 months; taper after 3 months if effective	Extended-release capsule: 6 mg, 9 mg
Budesonide extended-release (Uceris®)	Generic, Salix	**Induction of remission in adults with active, mild to moderate ulcerative colitis:** 9 mg orally once daily for up to 8 weeks	Extended-release capsule: 9 mg
Budesonide delayed-release (Tarpeyo™)	Calliditas	**Reduction of proteinuria in adults with primary IgA nephropathy (IgAN) at risk of rapid progression:** **Adults:** 16 mg once daily for 9 months, reduce to 8 mg daily for ≥2 weeks when discontinuing	Delayed-release capsule: 4 mg
Cortisone	Chartwell	**Adults and Children:** 25-300 mg per day or on alternate days depending on specific condition treated	Tablet: 25 mg
Deflazacort (Emflaza®)	PTC	**Treatment of Duchenne muscular dystrophy (DMD):** **Patients 2 years of age and older:** 0.9 mg/kg/day; discontinue gradually if administered for more than a few days Tablets may be crushed and mixed with applesauce; consume immediately The oral suspension should be mixed with 3-4 ounces of juice (except grapefruit juice) or milk, administer immediately Unused drug should be discarded 1 month after opening the container	Tablet: 6 mg, 18 mg, 30 mg, 36 mg - Oral suspension: 22.75 mg/mL
Dexamethasone (Dex™)	Generic, Roxane, Levin, Plight, Xspire, Scite	**Adults:** 0.75 mg to 9 mg per day in 2-4 divided doses depending on condition treated **Children:** 0.03 to 0.3 mg/kg per day, in 2-4 divided doses	Tablets: 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, 6 mg Oral solution: 0.5 mg/5 mL Intensol oral solution: 1 mg/mL Various dose packs (Dex™, Taperdex™) available

Drug	Manufacturer	Dosage	Availability
Dexamethasone (Hemady®)	Acrotech	**Treatment of multiple myeloma:** **Adults:** 20 mg or 40 mg once daily, depending on treatment regimen as used in combination with other anti-myeloma agents	Tablet: 20 mg
Hydrocortisone (Cortef®)	Generic, Pfizer	**Adults:** 20-240 mg per day, in 2-4 divided doses depending on condition treated **Children:** 2-8 mg/kg per day in 3-4 divided doses	Tablet: 5 mg, 10 mg, 20 mg

also induce muscle wasting via the suppression of anabolic signaling pathways, such as PI3K-AKT-mTOR, while promoting autophagy and proteolysis. This shift leads to increased bone resorption, further exacerbating glucocorticoid-induced osteoporosis. Long-term GC therapy lasting more than 3 months increases the risk of vertebral fractures by 30%. Muscle weakness, thinning skin, and easy bruising are also common. Furthermore, glucocorticoids increase the risk of infections. Psychiatric effects like mood swings, insomnia, and even psychosis may occur in some patients. Other side effects include adrenal suppression, cataracts, and glaucoma with prolonged usage. Effective management strategies involve close monitoring, dose adjustments, and the implementation of preventive measures such as osteoporosis prophylaxis and the use of antacids and vaccines [10,22]. For bone health, bisphosphonates and denosumab can be used to mitigate the risk. However, there are no specific medications available to prevent other side effects such as skin thinning, obesity, or the increased risk of diabetes [10].

Future Directions in Glucocorticoid Therapy

Emerging strategies in glucocorticoid therapy focus on improving drug delivery to minimize off-target effects. Liposomal and nanoparticle-based delivery systems are being developed to enhance tissue specificity, allowing for higher concentrations of glucocorticoids at inflamed sites while reducing systemic exposure. For instance, liposomal encapsulation of glucocorticoids has shown promise in mouse models of arthritis, where the targeted delivery to inflamed joints significantly reduced symptoms with minimal impact on surrounding tissues. This innovation offers hope for mitigating the well-known side effects of systemic glucocorticoid therapy, such as bone loss and muscle wasting, by refining their pharmacokinetics and delivery. Selective glucocorticoid receptor agonists (SEGRAs) are a novel class of glucocorticoid-like drugs that aim to dissociate the therapeutic anti-inflammatory effects from the adverse metabolic effects of glucocorticoid treatment. By specifically targeting the transrepression function of the glucocorticoid receptor, SEGRAs hold the potential to suppress pro-inflammatory pathways, such as NF-κB and AP-1 signaling, without triggering the transactivation mechanisms responsible for side effects like osteoporosis and hyperglycemia. Early clinical trials of SEGRAs, such as fosdagrocorat, have shown encouraging results in reducing inflammation with fewer side effects, offering a promising future direction for glucocorticoid therapy.

Conclusion

A deep understanding of glucocorticoid mechanisms, appropriate administration, and the application of chronotherapy is vital for optimizing treatment outcomes in inflammatory and autoimmune diseases. Tailoring glucocorticoid therapy to individual patient needs, aligning with biological rhythms, and choosing the most appropriate administration routes allows for maximal therapeutic benefit while minimizing adverse effects.

Author contribution

Study conception and design: HB, ÖK; draft manuscript preparation: HB, ÖK. All authors reviewed the results and approved the final version of the manuscript.

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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