Glucocorticoid use in rheumatology: a review

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Abstract

Background: Glucocorticoids play a pivotal role in the management of many rheumatologic diseases. However, glucocorticoid usage is associated with numerous adverse effects that involves almost all the major organ systems in the body. Hence, there is a need to balance the benefits and risks of glucocorticoids. There is also ongoing research for newer drugs with glucocorticoids actions with no or minimal adverse effects.

Objective: The aim of this literature review is to address the mechanism of action, pattern of use of glucocorticoids in various inflammatory arthritis and the adverse effects of glucocorticoids.

Data source: The literature review uses medical science based literature published locally and internationally on use of glucocorticoids in rheumatological diseases.

Conclusion: Glucocorticoids are very effective in the management of rheumatologic diseases. However, their use is curbed by the occurrence of adverse effects. These adverse effects can be abated if glucocorticoids are used prudently. There is no absolutely safe dose of glucocorticoids, only relatively safer doses. The clinical use of newer glucocorticoid drugs with no adverse effects will not occur in the near future.

Key words: Glucocorticoids, Rheumatology, Mechanism of action, Adverse effects, Pattern of glucocorticoid use, New glucocorticoid formulations

Introduction

Glucocorticoids play an important role in the management of rheumatologic diseases. It was discovered seven decades ago, when Philip Hench reported its dramatic effect on a young lady suffering from severe rheumatoid arthritis[1]. It is the most frequently used anti-inflammatory drugs despite the development of DMARDs and biological agents. However, its use is curbed by occurrence of adverse effects. This article summarizes the current use of corticosteroids in rheumatology.

Mechanism of action

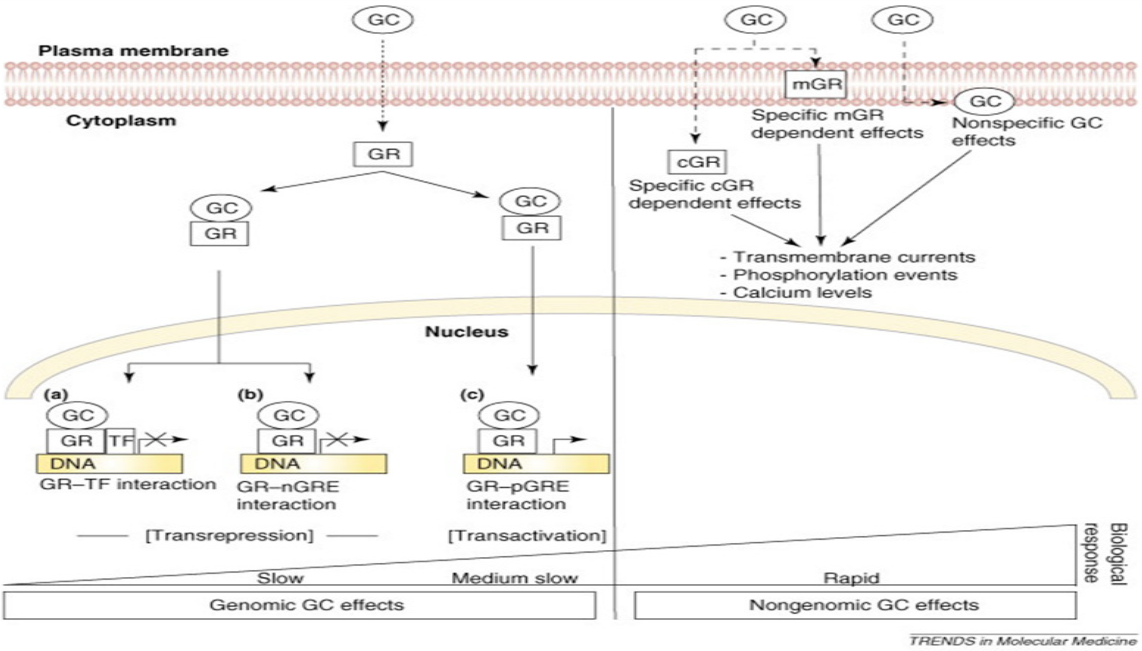
The effects of glucocorticoids are mediated by different mechanisms[2]. Two main mechanisms include the classic genomic and the non-genomic mechanism (Figure 1). The classic genomic mechanism is the most important mechanism of action in low dose therapy while the non-genomic mechanism is important in high dose therapy.

In the classic genomic mechanism, the glucocorticoid molecule enters into the cytoplasm whereby it binds to the cytosolic Glucocorticoid Receptor (GCR). This forms an activated glucocorticoid-GCR complex, which translocate into the nucleus and initiates transactivation and transrepression.

Transactivation occurs when two activated glucocorticoid-GCR complex form a dimer and bind to the glucocorticoid responsive element upregulating regulatory proteins synthesis. These proteins are responsible for the metabolic and some anti-inflammatory effects. In transrepression, the glucocorticoid-GCR complex inhibits transcription of proinflammatory transcription factors like nuclear factor kb. This process down-regulates pro-inflammatory protein synthesis[2].

Genomic processes require about thirty minutes for changes to occur in synthesis of regulatory protein, and takes hours to days for changes to occur at cellular or organ level. It was thought that the anti-inflammatory property of glucocorticoid was due to transrepression while the metabolic effects were due to transactivation[3]. However, recent studies state that some anti-inflammatory effects are caused by transactivation. Non-genomic effects are evident within minutes because they do not require protein synthesis. These effects are mediated by the cytosolic and membrane bound glucocorticoid receptors[2].

Figure 1: Genomic and non-genomic mechanism of glucocorticoids



Abbreviations: cGR = cytosolic Glucocorticoid Receptor; GC = Glucocorticoid; GRE = Glucocorticoid Receptor Responsive element; MAPK = Mitogen Activated Protein Kinase; Mgr = Membrane-bound glucocorticoid receptor; TCR = T-Cell Receptor; TF = Transcription Factor

Classification of glucocorticoids

The systemically used glucocorticoids are classified according to potency, mineralocorticoid effect and the duration of hypothalamic-pituitary-adrenal axis suppression (Table 1). Potency and mineralocorticoid activity is expressed relative to hydrocortisone. This helps in determining comparable doses. The steroid molecule in glucocorticoids is structurally modified so as to increase the potency and to minimize the mineralocorticoid effect[4].

Based on the duration to suppress the hypothalamic-pituitary-adrenal axis, the glucocorticoids are classified as short, intermediate and long acting. The duration of action is not well correlated with the duration of effect possibly because of the intracellular mechanisms. The actual therapeutic effect is longer[5].

Table 1: Classification of glucocorticoids according to potency, mineralocorticoid effect and the duration of hypothalamic-pituitary-adrenal axis suppression

Medication	Anti-inflammatory potency (relative)	Equivalent potency (mg)	Duration of effect (hyothalamic-pituitary-adrenal axis) (h)	Mineralocorticoid potency (relative)
Short acting				
Hydrocortisone	1	20	8-12	1
Intermediate acting				
Prednisone	4	5	18-36	0.8
Prednisolone	4	5	18-36	0.8
Methylprednisolone	5	4	18-36	0.5
Long acting				
Dexamethasone	25	0.75	>36	0

Pattern of glucocorticoid use

The dose, duration and administration of glucocorticoids depends on the diagnosis, clinical indication and goal of treatment. The potency of the drug is expressed in relation to the dosage. The definitions of low dose therapy through to pulse therapy is presented in Table 2[6].

Table 2: Definition of terms for glucocorticoid dosages

Dose	Definition
Low	≤7.5mg prednisone equivalent/ day
Medium	>7.5mg but ≤30mg prednisone equivalent/day
High	>30mg but ≤100mg prednisone equivalent/day
Very high	>100mg prednisone equivalent/ day
Pulse therapy	≥250mg prednisone equivalent/ day for 1 day or a few days

Primary immunosuppressive treatment with glucocorticoids

Glucocorticoids are pivotal in the management of systemic vasculitis, myositis and polymyalgia rheumatica. In polymyalgia rheumatica, monotherapy with glucocorticoid at 15mg prednisone or equivalent daily can achieve remission[7].

Glucocorticoids plays an important role in the management of giant cell arteritis. Empiric high dose pulse therapy of glucocorticoids should be initiated on suspicion of giant cell arteritis with acute visual loss or ischemic stroke. This should be followed by high dose maintenance oral prednisone or equivalent[8].

Pulse therapy

Pulse therapy is the administration of high glucocorticoid doses over a short period of time. In connective tissue disorders, pulse therapy is indicated for treatment of flares or disease induction[9]. 1000mg of methylprednisolone given intravenously for a period of three days is the standard pulse dose.

High and medium doses

High dose glucocorticoids in addition to other immunosuppressive drugs like cyclophosphamide are the cornerstone in the treatment of systemic vasculitis[10]. Intermittent treatment with high dose is also beneficial in acute gout attacks. A five day course of 35mg prednisone improved pain scores in patients with acute gout[11].

Low dose

Low dose glucocorticoid with DMARDs is often utilized in the management of rheumatoid arthritis. Glucocorticoids use has led to improvement in both clinical parameters and acute phase reactions[12,13].

Very low doses of glucocorticoids (<5mg of prednisone or equivalent) can sustain remission in patients with rheumatoid arthritis with minimal adverse effects[14]. A prospective study to validate the risk-benefit ratio of this study is currently ongoing[15].

Numerous studies have reported that the use of low dose glucocorticoids in early rheumatoid arthritis has a disease modifying effect[16,17]. The disease modifying effect or retardation of joint damage persists for four years in spite of using low dose glucocorticoids for a period of two years[18].

Local application of glucocorticoids

Intraarticular injection of glucocorticoids can be considered in patients with persisting non-infective arthritis. The effectiveness of this treatment depends on numerous factors like the joint involved, the severity of arthritis, amount of synovial fluid and the injection technique[19]. Triamcinolone hexacetonide was shown to have the longest effect[20].

Adverse effects

Glucocorticoids can cause frequent and serious adverse events. The adverse effects occur more frequently with prolonged use of high doses of glucocorticoids although some patients get these adverse effects at low doses[21]. However, there is scarcity of high quality data on the occurrence of adverse effects of glucocorticoids as most of the studies on glucocorticoid toxicity are either observational or retrospective[22]. This is further confounded by the fact that the adverse effects caused by glucocorticoids cannot be differentiated from complications of the disease or as other comorbidities. The adverse effects can be avoided or managed appropriately if glucocorticoids are used wisely.

Osteoporosis

Osteoporosis is a debilitating complication of glucocorticoid. The major risk factors are cumulative dose and the duration of glucocorticoid use[23]. Prolonged exposure to doses as low as 2.5mg – 5mg can increase the risk of vertebral fractures. Glucocorticoids almost doubles the risk of vertebral fractures. At least one patient out of four who have been on long term glucocorticoid develop a low energy fracture[24].

Bone loss occurs almost immediately after initiation of glucocorticoids. It mostly affects the vertebral bones because of its high trabecular content[25]. It also changes the architectural integrity of the bone.

Currently, there are effective prevention and treatment options, which can result in reduction of morbidity and mortality associated with glucocorticoids induced osteoporosis[26]. If glucocorticoids are meant to be given for more than three months, a baseline bone mineral density should be measured and then repeated annually. Glucocorticoid induced osteoporosis can be prevented by using the minimal effective glucocorticoid dose, calcium and Vitamin D supplementation in addition to physical activity. Active osteoporosis is usually treated using anti-resorptive drugs like bisphosphonates.

Avascular necrosis of bone (osteonecrosis)

About forty percent of patients on long term high doses of glucocorticoids present with osteonecrosis of the bone[27]. Patients usually present with persistent joint pains and decreased range of motion. Treatment mainly involves joint replacement surgery and bisphosphonates[27].

Myopathy

The most common drug induced myopathy is caused by glucocorticoid. This is characterized by fatigue, painless muscle weakness and muscle atrophy. It can either be acute or chronic. Discontinuation of the glucocorticoid usually results in increased muscle strength within four weeks[28].

Effect on glucose metabolism

Glucocorticoids have a dose dependent effect on glucose metabolism. The development of *de novo* diabetes is uncommon. Patients with a history of glucose intolerance or diabetes have difficulty in controlling their blood sugar levels when started on glucocorticoids.

Glucocorticoid induced hyperglycemia is multifactorial and include increased age, obesity, family history of diabetes, and gestational diabetes. Dysglycemia may improve with dose reduction and usually reverses when the glucocorticoids are discontinued. However some patients may develop persistent hyperglycemia that may require treatment with anti-diabetic agents[29].

Dyslipidemia

Glucocorticoids increases the synthesis of Very Low Density Lipoprotein (VLDL) and accumulation in the liver. All types of abnormal lipid profiles have been reported with use of glucocorticoids and management should be based on general clinical practice[30].

Weight gain and Cushingoid features

Weight gain and Cushingoid features are troubling side effects of glucocorticoids. It has been reported that there is a 4-8% increase in body weight when doses as little as 5mg of prednisone or equivalent are used for two years[31].

Adrenal suppression

Long term use of glucocorticoids leads to adrenal gland suppression due to hypothalamic pituitary axis suppression. Patients on chronic glucocorticoids may have an Addisonian like crisis if the glucocorticoids are discontinued abruptly or tapered off quickly[32]. Clinical AS tends to occur after glucocorticoid exposure for more than two weeks. Higher dose of glucocorticoids is a known risk factor.

In order, to prevent Addison crisis in patients undergoing chronic glucocorticoid therapy, it is recommended that the steroid are tapered or weaned off slowly. Glucocorticoid withdrawal should never be abrupt. Glucocorticoid withdrawal is indicated when their use is no longer indicated or when significant and uncontrollable side effects occur. Several tapering regimens have been published[33].

Patients who take any steroid dose for less than two weeks can abruptly stop treatment. They do not develop HPA axis suppression. The objective of tapering is to initially reduce the therapeutic dose (2.5mg every 3-4 days over a few weeks) to physiological dose (7.5mg / day prednisone or equivalent) and then proceed with further withdrawal to permit recovery of the HPA axis (1mg/d of prednisolone or equivalent every 2-4 weeks). This depends on the patient's general condition, until the medication is discontinued[34]. Other tapering regimens switch patient to alternate dosage of glucocorticoids before discontinuation[35]. Irrespective of tapering regimen used, if GC withdrawal syndrome, adrenal insufficiency or exacerbation of underlying disease occurs, the dose given at that time should be increased or maintained for a longer period of time.

Gastrointestinal side effects

Glucocorticoids increase the risk for gastritis, peptic ulcer disease and gastrointestinal bleeding. This risk rises when combined with a non-steroidal anti-inflammatory drugs[36]. Other gastrointestinal complications include visceral perforation, hepatic steatosis and acute pancreatitis.

Hypertension

The risk of hypertension increases by two fold in patients taking glucocorticoids. The risk is associated with cumulative dosage of glucocorticoids[21]. The risk of hypertension is higher in elderly patients. Hypertension occurs due to an imbalance between vasoconstriction and vasodilation further compounded by weight gain associated with corticosteroid use[37].

Cardiac side effects

There is a 2-4 fold increased risk of cardiovascular disease in patients using 7.5mg or more of prednisolone[38]. This is due to hypertension, dysglycemia and hypertriglyceridemia. Glucocorticoids also predispose to arrhythmias[39]. The cardiac adverse events are dose dependent and the risks decreases on discontinuation of the medicine. Rarely, intravenous pulse therapy with methylprednisolone has caused sudden death[40].

Dermatologic side effects

Chronic glucocorticoid usage causes skin atrophy by preventing secretion of collagen and hyaluronic acid by fibroblast[31]. This dermatoporosis is characterized by skin thinning and formation of telangiectasia and haematoma under the skin. This leads to poor wound healing with

subsequent loss of skin barrier function[41]. Higher doses of glucocorticoids causes steroid acne, hirsutism and hair loss[31].

Neuropsychiatric side effects

A varied number of neuropsychiatric symptoms can occur with glucocorticoids. They range from minor effects such as mood changes, irritability to major effects like depressive disorders, memory loss, psychosis, dementia and delirium[42]. The neuropsychiatric disorders are more common, about 52%, and most disturbing in patients who are taking more than 20mg of prednisone or equivalent for more than three months.

Initially, the patient experiences optimism, this is then replaced by depression. One in six patients will develop depression while on corticosteroids. Patients who take a short course of high dose corticosteroid tend to develop mania and hypomania rather than depression[43]. In majority of patients the symptoms resolve in 6 weeks after discontinuation of treatment. Furthermore, recovery is faster for patients with delirium than those with depression or psychosis[44].

Ophthalmologic side effects

The two common ophthalmologic adverse effects are cataract and glaucoma[45]. This risk increases with cumulative dose and treatment length. Cataracts occur in 11%-15% of patients on chronic glucocorticoid treatment[45]. However, some patients develop posterior sub capsular and cortical cataract even in doses less than 5mg/day[21]. Glucocorticoids increase intraocular pressure in 18%-36% of patients. This is worse in patients with prior glaucoma[31]. Glucocorticoids causes dysfunction of the trabecular meshwork hence unable to drain the aqueous humor[46]. The IOP returns to normal after discontinuation of glucocorticoids in 2-4 weeks. Other ophthalmologic side effects include mydriasis, ptosis, central serous chorioretinopathy, herpetic keratitis and cytomegalovirus retinitis.

Immunologic side effects

Chronic use of corticosteroids subdues cell mediated immunity and alters monocyte functions. This predisposes to intracellular infections[47]. The risk of infection increases with high doses. Corticosteroids makes patients vulnerable to viral, bacterial, fungal and parasitic infections. Furthermore, it can lead to reactivation of latent infections. Diagnosis may be challenging as unusual organisms may be involved and classic manifestations of infection may be masked.

New glucocorticoid formulations

Modified release prednisone

The symptoms of RA, namely joint stiffness, swelling and pain change in a circadian fashion. The symptoms are usually worse in the morning. This is because the levels of inflammatory cytokines are higher in the early hours of the day[48]. Modified Release (MR) prednisone is a new formulation of prednisone, that delays release of prednisone hence allowing adequate concentration of prednisone at night so as to mitigate the effects of increased pro-inflammatory cytokines at night. It significantly reduces interleukin 6 levels and morning symptoms when compared with control treatment. Furthermore, it does not increase the risk for adrenal suppression[49-51].

Liposomal glucocorticoids

Liposomal glucocorticoid is a modified drug delivery system whereby the drug is directly targeted to the synovial capsule[52]. Unlike, intra-articular injection, liposomal glucocorticoids are not rapidly cleared from the synovium into the circulation by virtue of their size and chemical composition[53]. This leads to less side effects as the drug is concentrated at the synovium with reduced exposure to non-target sites.

Selective GC Receptors Modulators (SGRM)

Glucocorticoids bind to glucocorticoid receptors whereby they may either cause transactivation or transrepression. Transrepression is mostly responsible for the anti-inflammatory effect while transactivation is responsible for the adverse effects of glucocorticoids. The SGRMs promote transrepression over transactivation[54], and hence have lesser metabolic adverse effects than the conventional glucocorticoids.

Recommendations for clinical practice

To ensure safe use of glucocorticoids in rheumatic diseases, several recommendations have been published. The main aim of these recommendations is to achieve optimal therapeutic glucocorticoid effect with minimal adverse effects as there is no absolute safe dose of glucocorticoid null of adverse effects. Certain measures can be undertaken so as to avoid or minimize the adverse effects of glucocorticoids.

Education

Patients should be informed about both the positive and negative effects of glucocorticoids over time. This alleviates unfounded fears, allows early recognition of true adverse effects and improves patients' compliance.

Preventive measures

All patients who are on medium to high dose glucocorticoids are at risk of osteoporosis. Calcium, and Vitamin D should be started with glucocorticoids, while those patients who are at high risk of osteoporosis, should also take bisphosphonates. Several studies have proved that calcium, vitamin D and bisphosphonates can both prevent and treat glucocorticoid induced osteoporosis[55,56].

Use in pregnancy

The fetus is protected from maternal glucocorticoids as glucocorticoid cannot traverse the placenta. Furthermore, cortisol and prednisolone are converted to inactive metabolites by the placental enzyme 11β hydroxysteroid dehydrogenase. However, some fetuses have intrauterine growth restriction, low birth weight or oral cleft when given antenatal steroids. It is advisable to avoid high dose steroids in the first trimester[57].

Conclusion

Glucocorticoids are very effective in the management of rheumatologic diseases. However, their use is curbed by the occurrence of adverse effects. There is no absolutely safe dose of glucocorticoids, only relatively safer doses. These adverse effects can be abated if glucocorticoids are used prudently. Clinical use of newer glucocorticoid drugs with no adverse effects will not occur in the near future.

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