Corticosteroids in Immunosuppression

Caroline Marzbani and Arvind Bhimaraj

Contents

Abstract

Corticosteroids have been utilized as mainstay pharmacological intervention for successful organ transplantation since the beginning. Several challenges exist in establishing a balance between achieving a tolerant atmosphere in the host immune system while minimizing the long-term impact of steroids on the body. Corticosteroids are used early in all solid organ transplantation but there is wide variability across various organs and centers in the duration of use and protocols of planned steroid wean. The adverse event profile of steroids is exhaustive and across many organ systems.

C. Marzbani · A. Bhimaraj (✉)
Department of Cardiology, Section of Advanced Heart Failure, Mechanical Support Devices and Cardiac Transplantation, Houston Methodist Hospital, Houston, TX, USA
e-mail: abhimaraj@houstonmethodist.org

H. J. Eisen (ed.), *Pharmacology of Immunosuppression,*
Handbook of Experimental Pharmacology 272, https://doi.org/10.1007/164_2021_567

Keywords

Immunosuppression · Organ transplantation · Steroids

1 Introduction

Corticosteroids are a general term used to describe a group of steroid hormones released by the adrenal cortex and their synthetic analogues. They are further classified into glucocorticoids and mineralocorticoids based on their physiological actions.

The corticosteroids used in transplantation medicine are generally glucocorticoids and used for their immune-modulatory actions on the immune system of the host with an objective to mitigate and minimize rejection. Glucocorticoids are one of the most widely prescribed drugs in the world and the worldwide market for glucocorticoids is estimated to be worth more than USD 10 billion per year (Ramamoorthy and Cidlowski 2016). While steroids alone did not make solid organ transplantation possible, they have been a mainstay background therapy and were the first class of medications that were used to achieve the objective of transplanting between immune non-compatible individuals.

2 Historical Perspective

The discovery of cortisone was centered around treatment of inflammatory disease, especially rheumatoid arthritis, which had debilitating symptoms and consequences prior to such discovery. Philip Hensch and Edward Kendall are credited with the discovery of cortisone and along with the Polish chemist Tadeus Riechtein received the Nobel Prize in Medicine and Physiology in 1950. Philip Hench, as a physician at Mayo Clinic published a series of 30 cases where symptoms of rheumatoid arthritis were relieved with the onset of jaundice, in pregnancy, infection, and surgery (Hench 1938). With a postulation that a "substance X" is secreted naturally in these conditions, and a hunch that it is coming from the adrenal glands, he collaborated with Edward Kendall, a professor of physiology and chemistry who was already studying adrenal hormones. While early work in their collaborative effort and independent work of their Polish competitor Reichten did not succeed in isolation of Cortin, the gloom of World War-II and a supposition of a need of steroid hormones as an anti-stress compound made isolation of and production of Cortin a U.S government priority (Kendall 1971). A culmination of efforts of these physician scientists with involvement of Merck led to the production of Cortisone in 1948. While no specific clinical indication was evident at that time, an insisting patient at Mayo Clinic made Hensch and Kendall try the medication leading to a sensational improvement of symptoms followed by documentation of the anti-inflammatory properties of the substance. As the world witnessed the balance of beneficial and adverse events of cortisone in various scenarios, early work in kidney transplant in

the 1960s revealed, validated, and propagated the ability of steroids to reverse acute rejection in living donor kidney transplant (Goodwin et al. 1962; Starzl and Marchioro 1963). A widespread use of corticosteroids as standard therapy for all kidney transplantation followed.

3 Mechanism of Action (Fig. 1)

Glucocorticoids manifest various immunomodulatory effects through genomic and non-genomic pathways. The genomic mechanism is mediated by binding to the intracellular glucocorticoid receptor (GR) which leads to conformational change in the ligand receptor complex followed by translocation of the complex into the nucleus. In the nucleus, this complex modulates the transcription of specific DNA sequences that lead to inhibition of the synthesis of almost all known inflammatory cytokines by blocking the function of transcription factors, such as nuclear factor-kappa-B (NF-kB) and activator protein-1 (AP-1), two common proinflammatory mediators (Scheinman et al. 1995; Auphan et al. 1995; Rhen and Cidlowski 2005). The GR/Steroid complex also blocks the promoter site of interleukin (IL)-1-alpha and IL-1-beta (Zhang et al. 1997), promoting anti-inflammatory gene transcription of I-kappa-B-alpha, IL-1 receptor-II, lipocortin-1 (annexin 1), IL-10, alpha-2-macroglobulin, and secretory leukocyte-protease inhibitor (Scheinman et al. 1995; Auphan et al. 1995). Glucocorticoids also influence the post translational aspects of proinflammatory mechanisms by diminishing the stability of messenger RNA (mRNA) encoding IL-1, IL-2, IL-6, IL-8, tumor necrosis factor, and granulocyte-macrophage colony-stimulating factor (Tobler et al. 1992).The non-genomic actions of glucocorticoids involve physiochemical interactions with cytosolic GR or membrane-bound GR which unlike genomic effects do not require protein synthesis and occur within seconds to minutes of GR activation (Groeneweg et al. 2012).

Neutrophilia is common while using glucocorticoids as they increase their release from bone marrow and cause a reduction in expression of adhesion molecules on both leukocytes and endothelial cells. This is mediated by a decrease in synthesis and release of prostaglandin mediators of cell adhesion. In contrast, lymphocytes, eosinophils, mast cells, basophils, and dendritic cells decrease in number after administration of glucocorticoids. The total number of natural killer cells remains unchanged. A single dose of cortisol results in a 70% decrease in lymphocytes and a 90% decrease in monocytes, occurring 4–6 h after treatment and persisting for about 24 h. Cell numbers then rise 24–72 h after treatment (Pountain et al. 1993). The decrease in lymphocytes, monocytes, and eosinophils is due to redistribution of these cells rather than cell lysis, although certain types of activated T lymphocytes undergo glucocorticoid-induced apoptosis (Schwartzman and Cidlowski 1994). Glucocorticoids also reduce migration of monocytes and macrophages resulting in decreased tissue accumulation and slight increase in the blood level of these cells. The effect of steroids on monocyte and macrophage functions is variable. Macrophage phagocytosis and clearance of opsonized bacteria by the reticuloendothelial cells are diminished (Atkinson and Frank 1974). Expression of major

promoter of the gene.

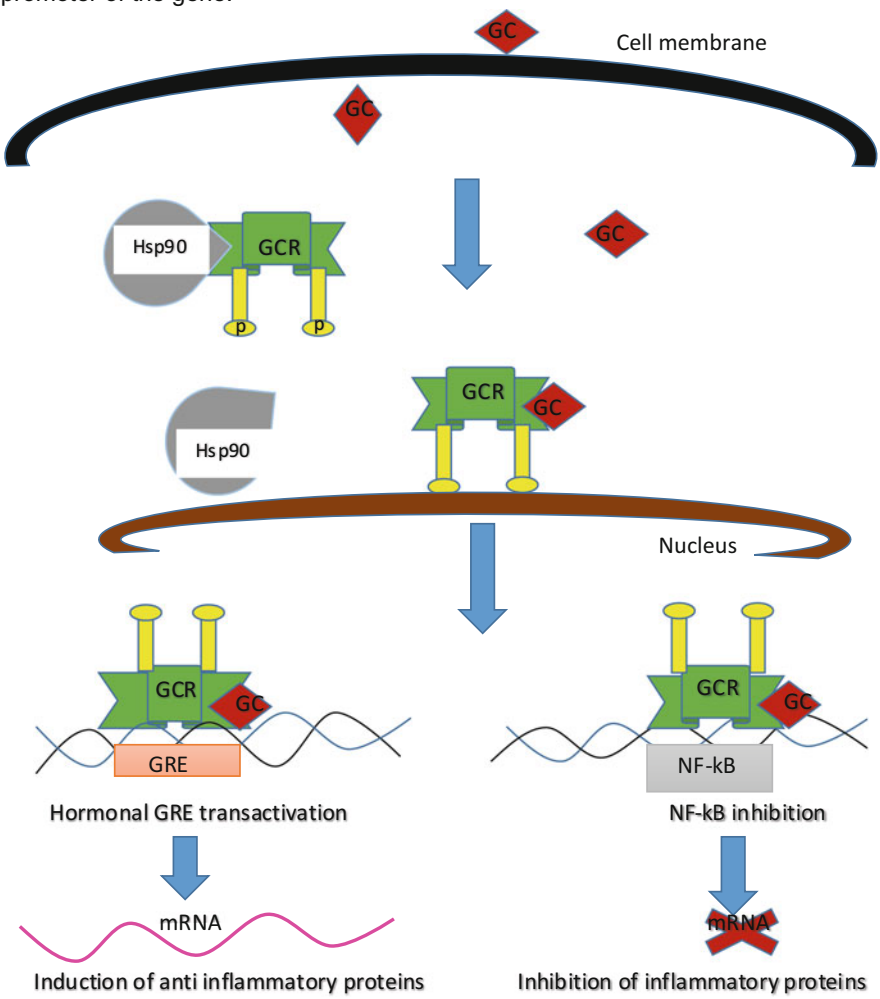

Fig. 1 Pictorial representation of mechanisms of action of glucocorticoids (GC). The GC (Red diamond shape) transverses the cell membrane to bind to the cytoplasmic GC receptor (GCR). This interaction frees the hsp-90 which is usually bound to GCR. The GC/GCR complex then is able to be transported into the nucleus where it impacts the transcription of various proteins through NFk-B inhibition and direct activation of the transcription of anti-inflammatory mRNA via glucocorticoid response element (GRE) which is a short sequence of DNA within the promoter of the gene

histocompatibility complex class I (MHC-I) and chemokine secretions are not affected or may in fact be increased in the presence of glucocorticoids. In contrast, the expression of MHC class II and antigen presenting function are reduced (Gerrard et al. 1984). The circulatory levels of B and T lymphocytes are reduced by glucocorticoids mainly because of redistribution of these cells to the

reticuloendothelial tissues and this effect is more pronounced on T cells than B cells. High doses of glucocorticoids inhibit immunoglobulin synthesis (Grayson et al. 1981) and decrease production of components of the complement system (Caren and Rosenberg 1966).

4 Types of Glucocorticoids and Dose

Glucocorticoids share the similar anti-inflammaory action and side effects. They differ in potency, duration, and mineralocorticoid activity. Prednisone is the most commonly used steroid. It is a prodrug and requires first-pass metabolism in order to be tranformed to the active metabolite, prednisolone. In patients with severe liver dysfunction prednisolone is preferred. Methylprednisolone differs in only a methyl group. Table 1 lists dose equivalents of the various glucocorticoids. Generally, in the context of solid organ transplant, for oral prednisolone, a low dose is considered up to 7.5 mg/d, medium dose >7.5 mg but <30 mg/d and high dose >30 mg but <100 mg/d, and very high dose is considered >100 mg/d. A pulse of methylprednisolone is considered between 250 and 1,000 mg/d for 1–3 days (Buttgereit et al. 2002).

5 Clinical Indications for Use in Solid Organ Transplant

5.1 Intraoperative Steroids

As an induction agent post solid organ transplant, steroids are used alone or along with other immunomodulatory agents intra-operation or immediately post-operation to initiate the process of adaptation or immunologic tolerance to the allograft. While

Table 1 Glucocorticoid comparisons and dose equivalents for glucocorticoid potency (Schimmer and Funder 2011)

Type of steroid	Dose equivalent for glucocorticoid potency	Mineralocorticoid potency	Half life
Cortisone	25	0.8	8–12 h
Hydrocortisone	20	1	8–12 h
Fludrocortisone	N/A	125	8–12 h
Prednisolone	5	0.6	18–36 h
Prednisone	5	0.6	18–36 h
Methylprednisolone	4	0.6	18–36 h
Dexamethasone	0.75	0	36–72 h

Table 2 Dose of intraoperative methylprednisolone at the time of solid organ transplant for different organs

Induction with methylprednisolone	Dose
Heart	1 g
Lung	1–1.5 g
Kidney and pancreas	200–500 mg
Liver	500 mg

steroids have been the mainstay of rejection prevention medications from the early days of transplantation, other potent induction agents like Thymoglobulin and IL-2 inhibitors have made steroids an adjunct treatment more than a primary induction strategy. The appropriate dose of intraoperative methylprednisolone has not been studied and various centers and organ programs use varying doses. Table 2 lists the dose of intraoperative methylprednisolone at our center. Typically, this intraoperative dose is followed by a gradual taper down to the maintenance dose over days to weeks depending on the dose started at and gradations of taper. Protocols range from starting at a high oral dose with a gradual long taper to others with an early transition to intravenous dosing followed by a higher decrement and faster wean down to maintenance dose. There are no studies comparing the various down titration regimens.

5.2 Maintenance Dosing and Steroid Withdrawal

The dose of steroids used to maintain immunological quiescence has decreased significantly from the advent of solid organ transplant: Most programs reach a maintenance dose of 5–10 mg of oral prednisone which is sometimes withdrawn completely after 6 months to 1 year after transplantation. While there has been a push towards steroid taper and wean in the context of minimizing long-term side effects of these medications, it is not clear if such a strategy makes a difference in the long-term outcomes for the graft or the patients across all organ groups. Also, it is not clear if the removal of the low dose of prednisone used in the current era mitigates the presumed side effects of prednisone in all patients while not increasing the risk on graft survival. While some centers tailor prednisone wean for those at lower immunological risk of rejection, some centers, more so in thoracic transplants, use steroids at the low maintenance dose for a lifetime (especially in lung transplants where rejection burden is high). While safety of steroid withdrawal has been established in many studies in all organs (Baran et al. 2011; Luan et al. 2009) especially in low rejection risk patients, the generalizability of such findings in individuals at a higher risk of rejection and a possibility of an unexpected trigger (like an infectious trigger) inciting acute rejection after achieving the so-called tolerant state off of steroids (Wang et al. 2010) have made universal adaptation of such strategy difficult. The strategy to withdraw maintenance steroids is also

confounded by the fact that clinical studies have varied in the timing of withdrawal and concomitant immunosuppressant medications. Despite all these controversies there seems to be some general principles that govern this decision: (1) Most low risk profile patients can be safely weaned off corticosteroids; (2) Steroid withdrawal with a background therapy of tacrolimus is considered to be safer than cyclosporine or only an mTOR inhibitor; (3) Early weaning is recommended: while steroid weaning is done within weeks in kidney transplants most thoracic programs do so in 6 months to 1 year; (4) While surveillance studies have focused on cellular rejection, recent acceptance and surveillance methods for antibody mediated rejection have left unanswered questions of the risk of AMR during the wean and careful surveillance is recommended. In our experience, withdrawal of steroids in patients who have been on prednisone for years seems to predispose them to AMR than ACR. The most commonly used tapering regimen includes (Saag and Furst 2019).

- 5–10 mg/day every 1–2 weeks from an initial dose above 40 mg of prednisone or equivalent per day.
- 5 mg/day every 1–2 weeks at prednisone doses between 40 and 20 mg/day.
- 2.5 mg/day every 2–3 weeks at prednisone doses between 20 and 10 mg/day.
- 1 mg/day every 2–4 weeks at prednisone doses between 10 and 5 mg/day.
- 0.5 mg/day every 2–4 weeks at prednisone doses from 5 mg/day down. This can be achieved by alternating daily doses, e.g., 5 mg on day one and 4 mg on day two.

5.3 Treatment in Acute Rejections

Methylprednisolone is the mainstay of treatment for acute cellular rejection (ACR) and has been adapted for basic therapy for antibody mediated rejection (AMR). ACR without overt organ derangement can sometimes be managed with increasing the dose of oral prednisone (in our institution, pathological 2R ACR in heart transplant with no graft dysfunction or hemodynamic derangements is treated with 100 mg prednisone daily for 3 days followed by a taper) while any suggestion of organ dysfunction is treated with an administration of intravenous pulse steroids. AMR is usually treated with high dose steroids with 500–1,000 mg methylprednisolone for 3–5 days while other strategies of antibody removal and B-cell suppression are being implemented.

6 Side Effects (Saag and Furst 2019)

Chronic steroid use has many physiological implications involving various organ systems. Many transplant patients a have other risk factors and are taking medications which can compound such effects of steroids. Table 3 lists the impact

Table 3 Impact of steroids on various organ systems of the human body that contributes to adverse effects in the setting of chronic long-term use

Organ system	Adverse effects
Skin	Skin atrophy, impaired wound healing, acne
General	Cushingoid appearance, weight gain
Eyes	Cataracts, glaucoma, exophthalmos, central serous chorioretinopathy
Cardiovascular	Fluid retention, hypertension, dyslipidemia, premature atherosclerotic disease, atrial fibrillation, atrial flutter
Nervous system	Stroke, pseudotumor cerebri, akathisia, psychosis, panic disorder, memory impairment, insomnia
Gastrointestinal	Gastritis, fatty liver, visceral perforation, pancreatitis
Bone and muscle	Osteoporosis, osteonecrosis, proximal myopathy
Endocrine	Hyperglycemia, secondary adrenal insufficiency
Infectious	Increased risk of bacterial, viral, and fungal infection

of glucocorticoids on various organ systems. Low doses of glucocorticoids (e.g., prednisone <5 mg/day) are associated with fewer adverse effects (Pincus et al. 2011), hence efforts are made to reduce dosing on the long term. Most glucocorticoid toxicity is at least partially reversible over time with early dose reduction (or withdrawal), detection, and treatment of contributing co-factors (Saag and Furst 2019). Skin ecchymosis and purpura often affect the sun-exposed areas of the dorsum of the hand and forearm. Acne, skin atrophy, impaired wound healing are common. Cataracts are common even with lower doses of <5 mg/day and is typically bilateral with posterior subcapsular involvement. Studies in non-organ transplant population using chronic steroids have shown an increase in adverse cardiovascular outcomes including fluid retention (e.g. glucocorticoids with mineralocorticoid property), hypertension, increased risk of premature atherosclerotic disease, stroke, heart failure, atrial fibrillation, atrial flutter, dyslipidemia and all-cause mortality. Cardiovascular disease risk is dose-dependent (Wei et al. 2004). It is unclear if this is true in the transplant setting due to inability to do a well-designed study to eliminate the influence of confounders. Glucocorticoid-induced reduction in ACTH release contributes to dyslipidemia by downregulating LDL receptors (Berg and Nilsson-Ehle 1996). Gastrointestinal effects can include peptic ulcer disease, gastritis, fatty liver, visceral perforation, and pancreatitis. The combination of glucocorticoids and NSAIDs results in a synergistic increase in the incidence of gastrointestinal events by two to fourfold increase. American College of Rheumatology (ACR) Task Force osteoporosis guidelines suggest that all patients taking glucocorticoids (any dose with an anticipated duration of ≥3 months) should maintain a total calcium intake of 1,000 to 1,200 mg/day and vitamin D intake of 600 to 800 international units/day through either diet and/or supplements to avoid osteonecrosis. Most studies have found that the risk of osteoporosis is low (<3%) in

patients treated with doses of prednisone <15–20 mg/day (Jones and Mont 2019). If patients are on long-term steroids most centers screen on regular intervals with DEXA scan. Myopathy is uncommon and typically presents with painless proximal motor weakness in both the upper and lower extremities. Other confounding medications like statins also need to be reviewed as culprit medications for myopathy. Mood disorders and emotional lability are more common in patients with a family history of depression or alcoholism. Psychosis occurs at high doses of prednisone usually above 20 mg/day and for prolonged periods while akathisia can occur even at low doses. Hyperglycemia is probably the most common and obvious impact of systemic glucocorticoids causing a dose-dependent increase in the level of serum blood glucose but the development of de novo diabetes in a patient with initially normal glucose tolerance is uncommon (Olefsky and Kimmerling 1976a). Risk factors for new-onset hyperglycemia during glucocorticoid therapy are thought to be the same as those for other patients, including a family history of diabetes, increased age, obesity, and a history of gestational diabetes (Olefsky and Kimmerling 1976b). Secondary adrenal insufficiency due to long-term use of glucocorticoids is more likely to develop due to suppression of the hypothalamic-pituitary-adrenal (HPA) axis in those who receive high doses (>20–30 mg prednisolone or equivalent) of systemic GCs for >3 weeks, those who develop Cushingoid features (Saag and Furst 2019) and those who have received an evening/bedtime dose of ≥5 mg of prednisone for many weeks. These patients should be treated like any patient with secondary adrenal insufficiency and if weaning of steroids is indicated should undergo tapering regimens. If these patients undergo minor stress while being on glucocorticoid treatment, they might require dose increase by double for 1–2 days and for severe stress three to tenfold dosage increase for 2–3 days. If steroids are used for <2–3 weeks, the recovery is expected and hence considered low risk for HPA suppression. Steroids can be stopped without taper in this scenario. In patients with intermediate risk using tapering regimens or HPA function test in certain case scenarios (e.g. planned elective surgery) could be beneficial (Table 4).

Table 4 Mineralocorticoid stress dose steroid dosing to be considered in situations of physiological stress

Stress (medical/surgical)	Steroid stress dose	Taper after the stress resolves
Minor, e.g., mild febrile illness, colonoscopy, <1 h anesthesia	25 mg or 30–50 mg/m^2 IV or PO hydrocortisone or equivalent	None
Moderate, e.g., pneumonia, multiple tooth extraction	50 mg or 50–75 mg/m^2 IV hydrocortisone or equivalent	Taper over 1–2 days
Major, e.g., severe burn, sepsis, major surgery	100 mg or 100 mg/m^2 IV hydrocortisone or equivalent	Taper over 1–3 days

7 Interactions of Glucocorticoids with Other Drugs (Liapi and Chrousos 1992)

Glucocorticoids can cause severe hypokalemia once given with other drugs such as Amphotericin B, diuretics, and can increase Digoxin toxicity. Glucocorticoids can decrease the blood level of some of the medications such as aspirin, warfarin, insulin, oral hypoglycemic agents and increase the blood level of cyclophosphamide or cyclosporine (Liapi and Chrousos 1992). Plasma levels of glucocorticoids can be decreased by use of antacids, cholestyramine or increased by cyclosporine, itraconazole, oral contraceptives. (Liapi and Chrousos 1992; Foisy et al. 2008; Saberi et al. 2013) Due to lack of a commercially available serum level for corticosteroids, it is not practical to adjust dosing despite potential pharmacokinetic interactions.

8 Conclusion

Glucocorticoids remain to be widely used in organ transplantation from organ induction to maintenance of immune quiescence, and treatment of acute rejection episodes. While long-term exposure can cause many deleterious effects, they remain a very useful armamentarium in post-transplant setting. Future studies need to focus on alternate delivery mechanisms that can have more targeted impact on the immune system while avoiding systemic side effects. Also, efforts to minimize dose-duration exposure to steroids need to be consolidated for better consensus. It is important to understand this class of drugs in the context of their role, pharmacokinetic, pharmacodynamics, adverse effects and clinical applications in order to utilize them appropriately to maintain transplanted organ vitality while preserving the rest of the body from the long-term impact of these medications.

References

Atkinson JP, Frank MM (1974) Complement-independent clearance of IgG-sensitized erythrocytes: inhibition by cortisone. Blood 44:629

Auphan N, DiDonato JA, Rosette C et al (1995) Immunosuppression by glucocorticoids: inhibition of NF-kappa B activity through induction of I kappa B synthesis. Science 270:286

Baran DA et al (2011) A prospective, randomized trial of single-drug versus dual-drug immunosuppression in heart transplantation the tacrolimus in combination, tacrolimus alone compared (TICTAC) trial. Circ Heart Fail 4:129–137

Berg AL, Nilsson-Ehle P (1996) ACTH lowers serum lipids in steroid-treated hyperlipemic patients with kidney disease. Kidney Int 50:538

Buttgereit F, da Silva JA, Boers M et al (2002) Standardized nomenclature for glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. Ann Rheum Dis 61(8):718–722

Caren LD, Rosenberg LT (1966) Steroids and serum complement in mice: influence of hydrocortisone, diethylstilbestrol, and testosterone. Science 152:782–783

Foisy MM, Yakiwchuk EM, Chiu I, Singh AE (2008) Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. HIV Med 9(6):389–396

Gerrard TL, Cupps TR, Jurgensen CH, Fauci AS (1984) Hydrocortisone-mediated inhibition of monocyte antigen presentation: dissociation of inhibitory effect and expression of DR antigens. Cell Immunol 85:330

Goodwin WE, Mims MM, Kaufman JJ (1962) Human renal transplantation. III. Technical problems encountered in six cases of kidney homotransplantation. Trans Am Assoc Genitourin Surg 54:116

Grayson J, Dooley NJ, Koski IP, Blaese RM (1981) Immunoglobulin production induced in vitro by glucocorticoid hormones. T cell-dependent stimulation of immunoglobulin production without B cell proliferation in cultures of human peripheral lymphocytes. Clin Invest 68: 1539–1547

Groeneweg FL, Karst H, de Kloet ER, Joels M (2012) Mineralocorticoid and glucocorticoid receptors at the neuronal membrane, regulators of nongenomic corticosteroid signaling. Mol Cell Endocrinol 350:299–309

Hench PS (1938) Effect of spontaneous jaundice on rheumatoid (atrophic) arthirtis. Br Med J 2(4050):394

Jones LC, Mont MA (2019) Uptodate

Kendall EC (1971) Cortisone: memoirs of a hormone hunter. Charles Scribner's Sons, New York

Liapi C, Chrousos GP (1992) Glucocorticoids. In: Jaffe SJ, Aranda JV (eds) Pediatric pharmacology, 2nd edn. WB Saunders, Philadelphia, pp 466–475

Luan FL et al (2009) Steroid-free maintenance immunosuppression in kidney transplantation: is it time to consider it as a standard therapy. Kidney Int 76(8):825–830

Olefsky JM, Kimmerling G (1976a) Effects of glucocorticoids on carbohydrate metabolism. Am J Med Sci 271:202

Olefsky JM, Kimmerling G (1976b) Effects of glucocorticoids on carbohydrate metabolism. Am J Med Sci 271:202

Pincus T et al (2011) Long-term prednisone in doses of less than 5 mg/day for treatment of rheumatoid arthritis: personal experience over 25 years. Clin Exp Rheumatol Incl Suppl 29(5):S130

Pountain GD, Keogan MT, Hazleman BL, Brown DL (1993) Effect of single dose compared with three days' prednisolone treatment of healthy volunteers: contrasting effects on circulating lymphocyte subsets. J Clin Pathol 46:1089–1092

Ramamoorthy S, Cidlowski JA (2016) Corticosteroids-mechanisms of action in health and disease. Rheum Dis Clin N Am 42(1):15–31

Rhen T, Cidlowski JA (2005) Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. N Engl J Med 353:1711

Saag KG, Furst DE (2019) Major side effects of systemic glucocorticoids. Uptodate

Saberi P, Phengrasamy T, Nguyen DP (2013) Inhaled corticosteroid use in HIV-positive individuals taking protease inhibitors: a review of pharmacokinetics, case reports and clinical management. HIV Med 14(9):519–529

Scheinman RI, Cogswell PC, Lofquist AK, Baldwin AS Jr (1995) Role of transcriptional activation of I kappa B alpha in mediation of immunosuppression by glucocorticoids. Science 270:283

Schimmer BP, Funder JW (2011) ACTH, adrenal steroids and pharmacology of the adrenal cortex. In: Brunton LL, Chabner BA, Knollmann BC (eds) Goodman and Gilman's the pharmacological basis of therapeutics, 12th edn. McGraw-Hill, New York

Schwartzman RA, Cidlowski JA (1994) Glucocorticoid-induced apoptosis of lymphoid cells. Int Arch Allergy Immunol 105:347–354

Starzl TE, Marchioro TL (1963) The reversal of rejection in human renal homografts with subsequent development of homograft tolerance. Surg Gynecol Obstet 117:385

Tobler A, Meier R, Seitz M et al (1992) Glucocorticoids downregulate gene expression of GM-CSF, NAP-1/IL-8, and IL-6, but not of M-CSF in human fibroblasts. Blood 79:45

Wang T, Ahmed EB, Chen L et al (2010) Infectionwith the intracellular bacterium, Listeria monocytogenes, overrides established tolerance in a mouse cardiac allograft model. Am J Transplant 10:1524–1533

Wei L, MacDonald TM, Walker BR (2004) Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann Intern Med 141:764

Zhang G, Zhang L, Duff GW (1997) A negative regulatory region containing a glucocorticosteroid response element (nGRE) in the human interleukin-1beta gene. DNA Cell Biol 16:145