



CORTICOSTEROIDS

Updated 2003 by Cecilia P. Chung and Anthony S. Russell.

History

1. Hench PS. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: (compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis: preliminary report. Mayo Clin Proc 24: 181-97, 1949.

Dr. Hench publishes his observations on the effect of cortisone in a patient with Rheumatoid Arthritis. This is the first report of therapeutic effects of glucocorticoids in Rheumatology.

Mechanisms

2. Morand AF, Goulding NJ. Glucocorticoids in rheumatoid arthritis – mediators and mechanisms. Br J Rheum 32: 816-819, 1993.

A better understanding of mechanisms that explain corticosteroid's therapeutic properties has not been matched by the development of "glucocorticoid like" drugs with greater specificity. The mechanism of action of corticosteroids is briefly reviewed highlighting the role of lipocortin 1 and lipocortin receptors as possible targets for rational and novel anti-inflammatory drugs. The importance of hypothalamo-pituitary-adrenal axis, because it is involved in the control of inflammation, is also stated.

3. Bamberger CM, Bamberger AM, Castro M, Chrousos GP. Glucocorticoid Receptor B, a potential endogenous inhibitor of glucocorticoid action in humans. J Clin Invest 95: 2435-41, 1995.

The authors study an isoform of human glucocorticoid receptor (hGR) called hGR-B that doesn't bind corticosteroids and is transcriptionally inactive. Using cell culture and plasmids they demonstrate that this molecule is able to inhibit the effects of hormone activated hGRa. The authors conclude that hGR-B would be an inhibitor of glucocorticoid action.

4. Scheinman RI, Cogswell PC, Lofquist AK, Baldwin AS. Role of Transcriptional Activation of IκBa in mediation of immunosuppression by glucocorticoids. Science 270: 283-286, 1995.

It is shown that glucocorticoids induce the transcription of the gene encoding the inhibitor of Nuclear Factor Kappa B subtype a (IκBa), this reduces the amount of NF-κB that translocates to the nucleus and pro-inflammatory cytokines secretion is decreased. As a consequence of that, the immune system is "blocked".

5. Barnes JP. Anti-inflammatory actions of glucocorticoids: molecular mechanisms: Clin Sci 94: 557-72, 1998.

Glucocorticoids are widely used to suppress inflammation. Anti-inflammatory mechanisms involving the glucocorticoid receptors, the glucocorticoid-responsive genes, and the release of anti-inflammatory molecules as lipocortin-1, IL-10, IL-1ra, nuclear factor-KB and the effect on cell function are discussed. Authors also review the effect on macrophages, eosinophils, lymphocytes, dendritic cells, neutrophils, endothelial cell and, epithelial cells. The author also discusses mechanisms of glucocorticoid resistance.

6. Buttgereit F, Wehling M and Burmester GR. A new hypothesis of modular glucocorticoid actions. Arthritis Rheum 5: 761-767, 1998.

Cytosolic receptor binding ends in the production (or inhibition) of several molecules e.g. lipocortin and proinflammatory cytokines. As those receptors are 63% saturated by 15 mg prednisone, other mechanisms mediate the need in some patients for much increased doses. This could involve hypothetical membrane receptors and such a model might explain intermediate dose effects. A third model might suggest that high doses of glucocorticosteroids (e.g. pulse therapy) produce direct physicochemical alteration of the membrane itself or of membrane associated proteins. This explains the observation that only very high doses of corticosteroids are successful in some major flares of immunologic diseases.

7. Newton R. Molecular mechanisms of glucocorticoid action: what is important? Thorax 55: 603-613, 2000.

Intracellular mechanisms related to corticosteroid's action are reviewed. The authors present the role of glucocorticoid receptors, the glucocorticoid response elements (GRE), genes and the use of transgenic mice in research. Finally, future directions in order to lead the characterization of new classes of glucocorticoids are suggested. The ideal glucocorticoid would be a molecule able to retain the anti-inflammatory effect while minimizing adverse events.

Therapeutics and adverse events

8. Boumpas DT, Chrousos GP, Wilder RL, Cupps TR, Balow JE: Glucocorticoid therapy for immune-mediated diseases: basic and clinical correlates. Ann Intern Med 119: 1198-1208, 1993.

Glucocorticoid's mechanisms of action, therapeutic use, complication of therapy and novel pharmacologic approaches are reviewed by the authors. Concepts as roles of glucocorticoid receptors, gene regulation, post-transcriptional effects, effects on inflammatory cells as well as therapeutic use and complications of therapy are explained in a very understandable way.

9. George, E and Kirwan JR. Corticosteroid therapy in rheumatoid arthritis. Bailliere's Clinical Rheumatology 4: 621-647, 1990.

The structure including a comparison between commonly used glucocorticoids in mode of action mainly explains the classical mechanisms that involve the receptor and the role of lipocortin. Pharmacology of synthetic steroids and clinical use of oral and Intraarticular glucocorticoids are reviewed.

10. Kirwan, JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. N Engl J Med 333: 142-6, 1995.

Fixed daily doses of 7.5 mg of prednisolone, given in addition to other treatments for a two-year period to 128 new rheumatoid patients are evaluated. The two primary outcomes were progression of damage using the Larsen score and the development of erosions. The author concludes that prednisolone reduces the rate of radiological progression, but did not affect symptoms at 2 years.

11. Kirwan JR, Russell AS. Systemic glucocorticoid treatment in rheumatoid arthritis – a debate. Scand J Rheum 27: 247-251, 1998.

The authors discuss arguments for and against the use of oral corticoids in Rheumatoid Arthritis patients. Benefits, e.g. improvement in symptoms and slowing of erosions; as well as adverse events, are highlighted.

12. Da Silva JA, Bijlsma JW. Optimizing glucocorticoid therapy in rheumatoid arthritis. Rheum Dis Clin North Am 26: 859-880, 2000.

This article reviews the action of glucocorticoids (GC). These may impact the cytokine network via binding to Cytosolic receptors and subsequent regulation of cytokine gene transcription. Factors possibly underlying GC resistance are also reviewed.

13. Kirwan JR. Systemic low-dose glucocorticoid treatment in rheumatoid arthritis. Rheum Dis Clin North Am. 27: 389-403, 2001.

Dr. Kirwan reviews the clinical and radiological efficacy of glucocorticoids, their potential adverse events and suggests a treatment strategy for their use. Studies regarding the efficacy of glucocorticoids in clinical symptoms are mentioned, showing that the use of corticosteroids improves clinical symptoms and disability, but just in the first months of treatment. The author also discusses several papers, including his study of prednisolone 7.5 mg per day and the recent information from the COBRA study, both show efficacy of glucocorticoids in slowing radiographic progression. The issues of increased risk of mortality, symptomatic toxicity and flares after cessation of treatment for glucocorticoids-treated patients are also mentioned. Adverse events such as infections, peptic ulceration, osteoporosis and atherosclerosis are analyzed. Finally, the author suggests a treatment strategy based on using corticosteroids for symptoms as a short term therapy for specific reasons and also using them for preventing radiological damage just in the first years.

14. Cooper C, Kirwan JR. The risks of local and systemic corticosteroid administration. *Bailliere's Clinical Rheumatology* 4: 305-332, 1990.

Adverse event profiles of oral, pulsed intravenous and intraarticular steroids are analyzed. The association between oral corticosteroids and metabolic effects, predisposition to infection, musculoskeletal complications, peptic ulcers, growth retardation, atherosclerosis, suppression of the hypothalamic-pituitary-adrenal axis, as well as ophthalmologic, nervous and dermatological complications are reviewed. The association between pulsed intravenous corticosteroids with sudden death, arrhythmias, hyperglycemia, psychosis, severe infections, and pancreatitis are mentioned. Infectious arthritis, tendon rupture, destructive arthritis, post injection synovitis, cutaneous complications and cartilage destruction are mentioned as complications related to intraarticular corticosteroids.

15. Saag K, Konhne R, Cadwell JR et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: An analysis of serious adverse events. *Amer J Med* 96: 115-123, 1994.

This is a study that included 112 RA patients on low dose (6,1 +/- 3.1 mg/d) long-term (6.2 +/-4.6 years) prednisone compared to 112 matched RA patients not using corticosteroids. More adverse events were seen in the corticosteroid group, including fractures, serious infections and GI bleeds.

16. Gourley MF, Austin HA III, Scott D et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with Lupus Nephritis. *Ann Intern Med* 125: 549-557, 1996.

This is a randomized controlled trial with at least 5 years of follow-up that included 82 patients with lupus nephritis with proliferative nephritis. Authors compared IV bolus of methylprednisolone (1 g/m² body surface area) given monthly for at least one year, cyclophosphamide (0.5 – 1 g/m²) given monthly for 6 months and then quarterly; or bolus therapy with both cyclophosphamide and methylprednisolone. All patients were on prednisone 0.5 mg/kg per day per 4 weeks then tapered. Monthly boluses of methylprednisolone were less effective than monthly cyclophosphamide. A trend toward greater efficacy with combination was seen.

17. Zonana-Nacach A, Barr SG, Magder LS and Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum* 43: 1801-1808, 2000.

The contribution of corticosteroid therapy to organ damage is evaluated in 539 SLE patients. Cox proportional hazards models showed that cumulative prednisone dose was associated with adverse events such as osteoporotic fractures, coronary artery disease, cataracts and avascular necrosis. A further analysis showed that the risk of avascular necrosis and stroke was increased in relation to high-dose prednisone.

18. Cunnane G, Lane N. Steroid-induced osteoporosis in systemic lupus erythematosus. *Rheum Dis Clin North Am* 26: 311-329, 2000.
Patients with SLE are at risk of osteoporosis because of the disease itself and because of glucocorticoid therapy. This article reviews the mechanisms of steroid-induced osteoporosis and suggests guidelines for management as current therapy and potential therapeutic options.

19. Delecoeuillerie G, Joly P, Cohen de Lara A, Paolaggi JB. Polymyalgia rheumatica and temporal arteritis: a retrospective analysis of prognosis features and different corticosteroid regimens (11 year survey of 210 patients) *Ann Rheum Dis* 47: 733-739, 1988.

This is a retrospective study of 210 patients with polymyalgia rheumatica (PMR) and/or temporal arteritis (TA) treated with prednisone 15 mg/d. Authors conclude that PMR is a benign disease requiring low dose corticosteroids and that some patients with TA could be treated with low dose corticosteroids as well.

20. Langford C, Talar-Williams C, Barron KS, Sneller MC. A staged approach to the treatment of Wegener's Granulomatosis. *Arthritis Rheum* 42: 2666-2673, 1999.

This is an open-label, prospective, trial of 31 Wegener's patients that tested oral cyclophosphamide 2 mg/kg/d and prednisone 1 mg/kg/d for remission and methotrexate for maintenance. Glucocorticoids were discontinued in a mean of 8 months. No patients died, 5 had relapses and 2 withdrew as a result of toxicity.

21. Guillevin L, Cohen P, Mahr A et al. Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide (CYC) pulses in sixty-five patients. *Arthritis Care and Research* 49: 93-100, 2003.

Two regimens of combined therapy were compared in 65 patients with PAN or MPA with poor prognosis factors. Both regimes included glucocorticoid as daily pulse of 15 mg/kg for 3 days and then 1 mg/kg/day orally for 3 weeks then tapered. CYC was administered every two weeks for one month, then every four weeks, patients were randomly assigned to receive 6 or 12 pulses. Patients that receive corticosteroids plus 12 pulses of CYC had better outcomes.

22. Weinstein RS. The pathogenesis of Glucocorticoid-induced Osteoporosis. *Clin Exp Rheumatol* 18 (Suppl 21): S35-40, 2000.

The author presents several mechanisms to explain glucocorticoid-induced osteoporosis. Decreased bone formation, diminished intestinal calcium and urinary calcium reabsorption, secondary hypogonadism or hyperparathyroidism are proposed. The effect on osteoblastogenesis and the increased apoptosis of osteoblasts and osteocytes are also reviewed.

23. Boulos P, Adachi JD. Guidelines for the prevention and therapy of glucocorticoid-induced osteoporosis. . Clin Exp Rheumatol 18 (Suppl 21): S79-S86, 2000.

This is a review of all randomized controlled trials studying prevention or treatment of glucocorticoid-induced osteoporosis. Calcium and vitamin D, hormonal therapy, calcitonin, parathyroid hormone, fluoride and bisphosphonates are discussed. Authors suggest the use of bisphosphonates as a treatment of choice for prevention and management of glucocorticoid-induced osteoporosis.

24. Piper JM, Ray WA, Daugherty JR et al. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 114: 735-740, 1991.

Corticosteroids alone don't increase the risk of hospitalization for peptic ulcer or gastrointestinal bleeding, but when taken together with NSAIDs the risk of bleeding increases markedly, with an estimated relative risk of 4.4 (C.I. 2.0-9.7).

New approaches

25. Markham A Bryson HM. Deflazacort. A review of its pharmacological properties and therapeutic efficacy. Drugs 50: 317-333, 1995.

Deflazacort is an oxazoline derivative of prednisolone with anti-inflammatory and immunosuppressive activity. It is as effective as prednisone or methylprednisolone in patients with rheumatoid arthritis. Gastrointestinal symptoms are the most common adverse events in deflazacort . It is thought to have less serious metabolic sequela.