Review article

THE MECHANISM OF ACTION OF ORAL CORTICOSTEROIDS IN RELATION TO SHORT- AND LONG-TERM-BURST THERAPY

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ABSTRACT

Corticosteroids, potent anti-inflammatory agents, are broadly used in various inflammatory and immune-dependent pathologies, which include asthma. Through non-genomic and genomic mechanisms of action, corticosteroids reduce pro-inflammatory mediators while promoting anti-inflammatory molecule expression. Furthermore, in the context of asthma treatment, they also promote the expression of β2 adrenergic receptors which increase the therapeutic potential of β2-receptor agonists to promote bronchodilation. However, corticosteroids also precipitate a variety of adverse events which reduce the quality of life of patients and predispose them to further pathological alterations. Given the ubiquitous expression of the glucocorticoid receptor, alongside the non-genomic and genomic mechanisms of corticosteroids, a myriad interconnecting physiological processes are altered upon receptor modulation. Both long- and short-course treatment has been linked to immune suppression, metabolic and cardiovascular disease, cerebrovascular accidents, osteoporosis, ophthalmic disorders, pneumonia and mood disorders. Consequently, clinical decision-making should consider the potential risks involved in short- and long-term use of corticosteroids because pathophysiological changes may be precipitated in both.

Keywords: anti-inflammatory, corticosteroids, mechanism of action, transactivation, transrepression

INTRODUCTION

Inflammation is an innate biological mechanism that facilitates the host's control of infectious and injurious threats; however, it must be regulated to avert damage to the host tissue. Homeostatic control is therefore crucial to preventing increased susceptibility to infection and malignancies, on the one hand, and allergic and autoimmune manifestations, on the other. Corticosteroids are naturally occurring key regulators of homeostasis and, while their properties were already widely known by the turn of the previous century, difficulties with extraction precluded their exogenous use until the late 1940s.

The initial administration of the first synthesised corticosteroids, 'Substance X' (also known as 'Compound E'), to patients with rheumatoid arthritis by Philip Showalter Hench at the Mayo Clinic in 1948 yielded remarkable results. Patients experienced a complete remission of symptoms and previously bedridden individuals demonstrated sudden mobility. However, the enthusiasm surrounding this miracle drug, called 'Nature's dramatic antidote', was short-lived, as symptoms recurred once the injections were stopped.[1]

Continuous dosing also resulted in a host of side effects:

> Olsen's reaction to the drug came quickly. Her face grew pale and swelled like the moon. Her periods stopped. Some days she gained four, maybe seven pounds. But Olsen wasn't the only one whose body went haywire. Some of his [Hench's] trial patients were overtaken by euphoria, others by psychosis. They became dizzy and disoriented. Their blood pressure fluctuated as rapidly as Olsen's weight.[2]

Upon receiving the Nobel Prize in 1950 for the discovery of cortisone, along with Edward Kendall and Tadeus Reichstein, Hench cautioned physicians against prescribing the drug before fully comprehending its risks, limitations and applications.[1] This admonition remains pertinent in the present day. Notably, significant advances have been made over the past seven decades, particularly regarding our understanding of the mechanisms of action of cortisone and its effects on the immune system and other organ systems. These aspects are briefly reviewed in this article.

GENOMIC AND NON-GENOMIC MECHANISMS OF ACTION OF CORTICOSTEROIDS

Corticosteroids provide a broad base of anti-inflammatory and immune suppressive biological properties, making them rational choices for pharmacotherapy in diseases with an inflammatory or an immune component.[3–6] However, depending on the pathology and the clinical considerations, their feasibility and safety should be assessed based on the evidence.

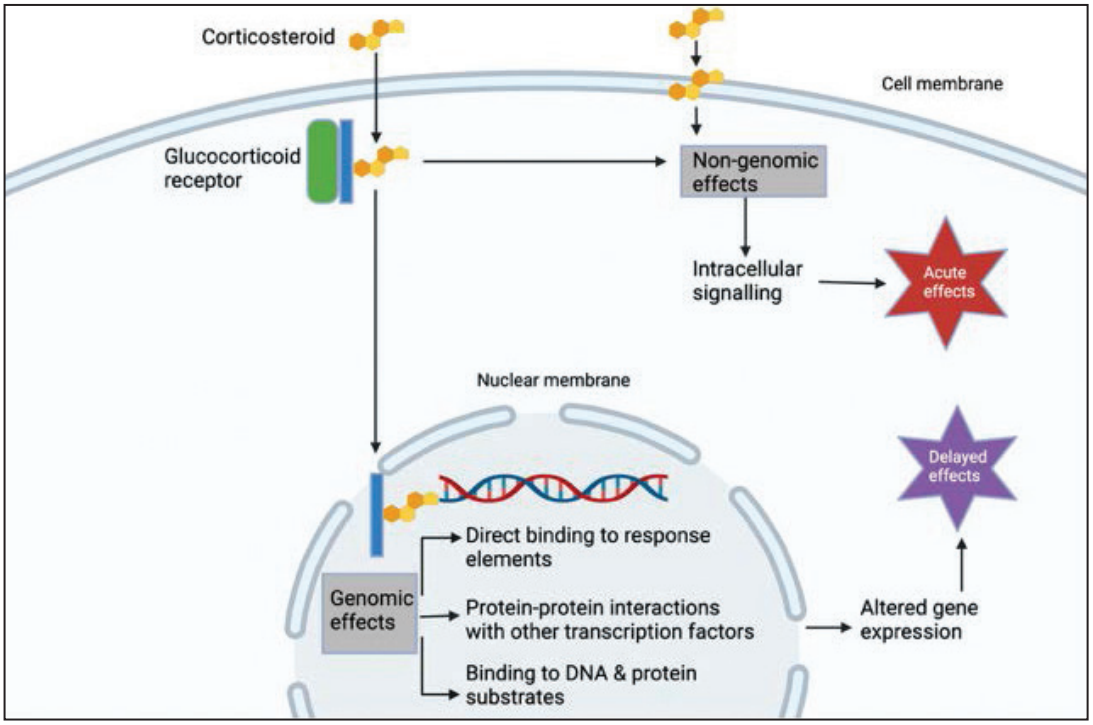

Figure 1: Genomic and non-genomic mechanisms of action of corticosteroids
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Corticosteroids present with non-genomic and genomic mechanisms that modulate their biological response as acute and delayed effects respectively.[3,6] Non-genomic effects may occur via membrane-bound receptors which promote associated intracellular signalling pathways, modulated largely by membrane-bound glucocorticoid receptors or together with the involvement of G-protein-coupled receptors and kinases.[4] Non-genomic effects appear within a very short time frame but they are not necessarily well understood.[4] Non-genomic effects should not be viewed in isolation from the slower genomic mechanisms, though, as their modulations support one another (see Figure 1).[6] Some studies have estimated that up to 20% of leukocyte genes are responsive to glucocorticoid receptor-mediated regulation.[7]

Corticosteroids are ligands for the glucocorticoid receptor.[4] Upon entering the cell, corticosteroids bind to and activate the cytoplasmic glucocorticoid receptor, which allows for its translocation to the nucleus.[4,6,8] Within the nucleus, activated glucocorticoid receptors interact with the glucocorticoid response element that modulates either positively (transactivation) or negatively (cis-repression or transrepression) the expression of inflammatory genes, including those controlling glucocorticoid receptor synthesis.[3,4,6] In doing so, the interaction allows the glucocorticoid receptor to associate with a series of proteins that modulate the gene expression of pro-inflammatory and anti-inflammatory mediators.[8,9] In general, transrepression is considered important for the therapeutic anti-inflammatory and immunosuppressive effects of corticosteroids, whereas cis-repression and, to some extent, transactivation is linked to its undesired adverse effect profile (see Figure 2).[5]

Transactivation is mediated by the glucocorticoid receptor being bound to response elements such as the glucocorticoid response element, which recruits coregulators to facilitate the process.[6] Interaction with transcription factors such as cyclic adenosine monophosphate response element-binding protein (CBP) reduces pro-inflammatory gene transcription.[4,9] Importantly, some binding positions on the DNA do not necessarily reflect an association with the glucocorticoid response element and therefore may also involve other promotors.[6] Several genes are induced which modulate anti-inflammatory molecules such as annexin 1, interleukin 10 (IL-10), inhibitor of nuclear factor-κB (NF-κB) (IκB-α), mitogen-activated protein kinase (MAPK) phosphatase, IL-1 receptor antagonist, IL-1 receptor-2, secretory leukocyte inhibitory protein and Clara cell protein; or they may promote expression of the β2-adrenergic receptor (see Figure 2).[4,5,9]

Transrepression is mediated by the direct interference of the glucocorticoid receptor with transcriptional factors via protein–protein interactions or by functional-negative glucocorticoid receptors that modulate promoter regions for gene repressesion.[6,8] Most of the anti-inflammatory properties appear to be mediated via transrepression.[10] For example, by interaction with the pro-inflammatory mediators such as activator protein-1 (AP-1) or NF-κB, signalling is reduced, which prevents inflammatory responses.[8,9] Furthermore, pro-inflammatory transcription factor expression may be reduced due to glucocorticoid response element binding, and either the anti-inflammatory IκB-α molecule may be expressed or glucocorticoid-inducible leucine zipper induction may reduce AP-1 binding to DNA.[8] The effects on the transcription of

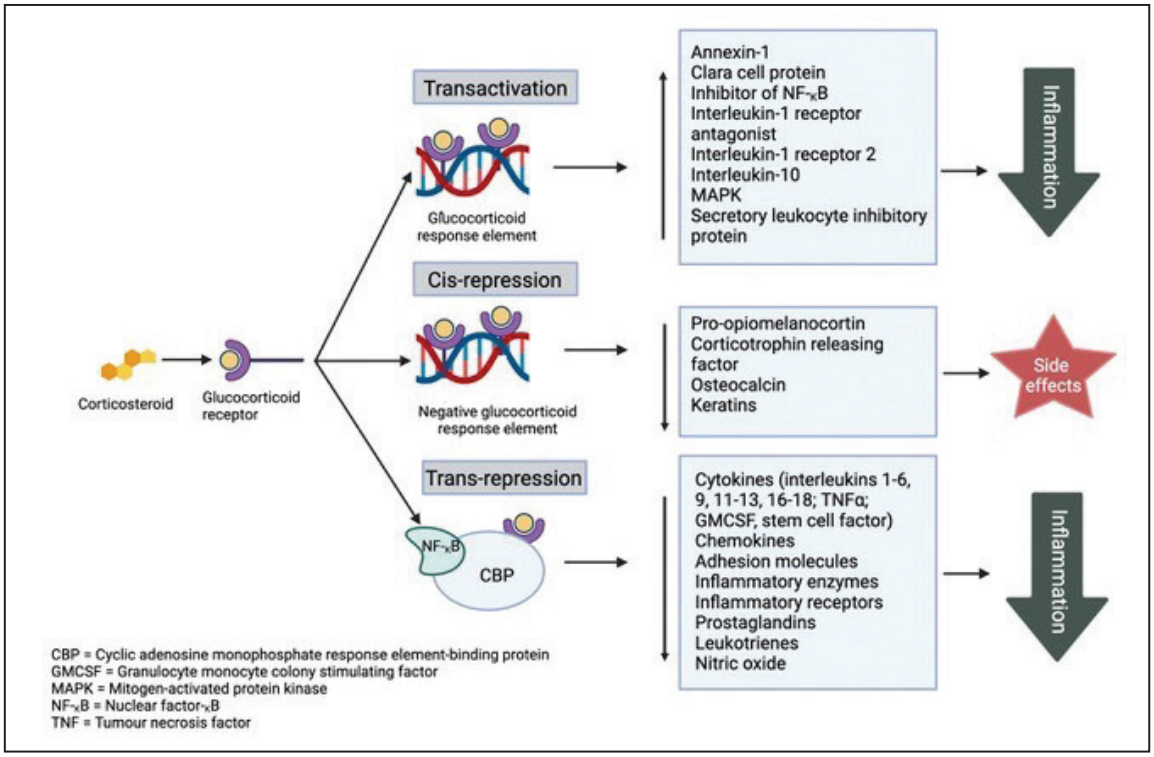

Figure 2: Transactivation and transrepression.
Corticosteroids influence gene expression through multiple mechanisms. After entering the cell, they bind to glucocorticoid receptors (GRs) in the cytoplasm, prompting their translocation to the nucleus. Once there, GRs attach to glucocorticoid response elements (GREs) in the promoter regions of steroid-responsive genes, leading to the production of antiinflammatory proteins. Additionally, GRs can bind to negative GREs, suppressing gene expression (cis-repression), a process associated with some of the common side effects of corticosteroids. In the nucleus, GRs also interact with coactivator molecules like CBP, which is activated by proinflammatory transcription factors such as NF-κB. This interaction inhibits the expression of inflammatory genes driven by these transcription factors. Created in BioRender. T Rossouw. (2024). BioRender.com/t78j002

genes are, however, cell-type-specific and therefore they differ across tissues due to the expression levels and the availability of coactivators or corepressors.[10] For example, in lung tissue, the glucocorticoid receptor-α isoform is active, whereas the glucocorticoid receptor-β isoform is inactive.[4] Consequently, differential expression of the two isoforms affects their receptiveness to corticosteroid therapy, where the glucocorticoid receptor-β isoform is often highly expressed in resistant or severe asthma patients.[4] Reduced transcription occurs, among other reasons, for various ILs (IL-1 to -6, IL-9, IL-11 to -13, IL-16 to -18), tumour necrosis factor-α, granulocyte macrophage colony-stimulating factor, stem-cell factor, inducible nitric-oxide synthase and cyclooxygenase and cytoplasmic phospholipase A2 (see Figure 2).[5,9]

IMPACT OF CORTICOSTEROIDS ON IMMUNE SYSTEM

Broadly speaking, inflammatory responses can be divided into three types. Type 1 is driven by T-helper (T_H)1 lymphocytes, macrophages, natural killer (NK) cells and innate lymphoid cells (ILC)1. Its main function is antiviral, antibacterial and antitumour responses. Type 2 inflammation has a predominance of T_H2 lymphocytes, basophils, mast cells, eosinophils and ILC2. It is involved in the humoral response against parasites and helminths and regulates wound repair. Type 3 is driven by T_H17 lymphocytes and neutrophils and is predominantly involved in maintaining the integrity of the gastrointestinal epithelial barrier and protection against extracellular bacteria and fungi. The dysregulation of Type 1 and 3 responses leads to various autoimmune manifestations, whereas dysregulation of Type 2 inflammation results in allergic diseases, such as Type 2 asthma (see Figure 3).

Corticosteroids exert a broad spectrum of effects on the immune system (see Table I). They induce the apoptotic cell death of developing thymocytes, as a result reducing the total number of T-lymphocytes. Their predominant effect is, however, to switch off multiple inflammatory genes (encoding cytokines, chemokines, adhesion molecules, inflammatory enzymes, receptors and proteins) that have been activated during the inflammatory process. In higher concentrations, they have additional effects on the synthesis of anti-inflammatory proteins and postgenomic effects.[7]

By modulating the expression of pro- and anti-inflammatory molecules, inflammatory cell recruitment and activation are reduced due to a decrease in the production of chemotactic factors and adhesion molecules.[9] Cells such as eosinophils, mast cells, dendritic cells and T-lymphocytes are therefore less available to mediate inflammatory effects in tissue, which prevents excessive immune responses.[9]

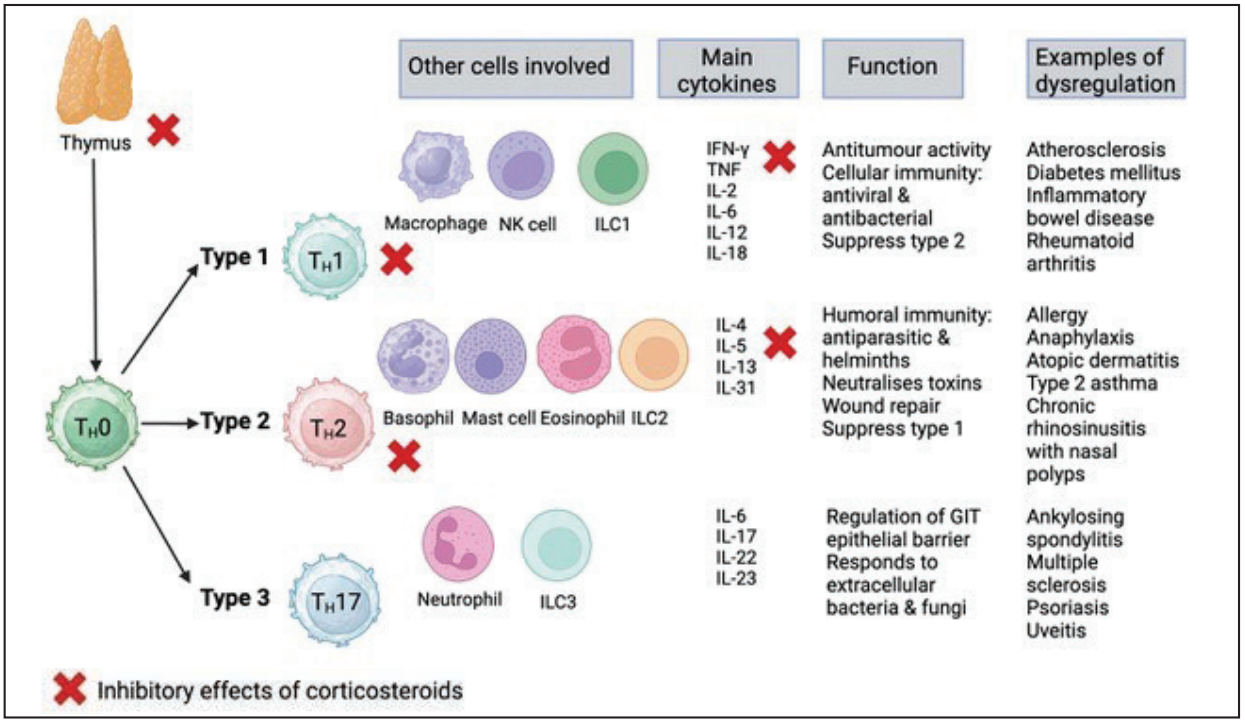

Figure 3: Inhibitory effect of corticosteroids on the immune system. Created in BioRender. T Rossouw. (2024). BioRender.com/t78j003

As a treatment for asthma, corticosteroids reduce the availability of inflammatory cells (eosinophils, T-lymphocytes, mast cells, macrophages, dendritic cells) through reduced cytokine secretion and the lower recruitment and/or induction of apoptosis.[9] Furthermore, corticosteroids reduce tissue leakage in endothelial cells, hinder mucus secretion from mucus cells, decrease cytokine release from epithelial cells and promote β2-adrenergic receptor expression in airway smooth muscle.[9] By reducing inflammatory responses, airway clearance is promoted, whereas β2-adrenergic receptor expression sensitises patients to β2-adrenergic receptor agonist therapy and promotes bronchodilation.[9,11] β2-adrenergic receptor agonists have also been shown to induce several genes associated with the expression of glucocorticoid receptors.[11]

Type-2 inflammation, reflected in high blood and sputum eosinophil counts, has consistently been associated with a significantly greater response to oral corticosteroid (OCS) therapy. Such therapy has been reported to reduce blood eosinophils by 76% (95% CI: 63–88) and sputum eosinophils by 89% (95% CI: 79–98). In contrast, OCS therapy resulted in only a moderate reduction in fractional exhaled nitric oxide (FeNO), which suggests that it is a more potent inhibitor of the IL-5 than IL-4/IL-13 pathway.[12] Markers of Type-2 inflammation return to baseline levels after approximately 4–8 weeks of OCS treatment.[13,14]

PROFILE OF ADVERSE EFFECTS

Since the glucocorticoid receptor is expressed throughout the body and since corticosteroids have diverse mechanisms of action, it is not surprising that its use has an impact on multiple interconnecting physiological processes.[15] As a stress-related response, this integrated function of corticosteroids is essential to maintaining homeostasis; however, it also increases the multi-organ adverse effects profile of such drugs when they are used systemically. Although inhaled corticosteroid therapy is a common practice in asthma treatment, OCS therapy is also considered, depending on the exacerbations or severity of the condition.[16] An inevitable concern with oral corticosteroid therapy is that the localised anti-inflammatory effect required for asthmatic control may be over-exerted, leading to the promotion of systemic immune suppression and corticosteroid toxicity.[16]

Extended exposure to corticosteroids or high-dose corticosteroid treatment is accompanied by a variety of adverse effects, including hyperglycaemia, lipodystrophy and weight gain, myopathy, osteoporosis, hypertension and arthrosclerosis, and adrenal suppression.[5,16] Psychiatric effects may include insomnia and behavioural alterations (such as mania, aggression and anxiety).[16] Immunosuppressant effects may perturb wound-healing or predispose individuals to opportunistic infections, while atrophy of the dermis and epidermis may reduce the integrity of the skin.[5]

CHRONIC VIRAL INFECTIONS

Given the impact of corticosteroids on Type 1 immune responses, chronic viral infections, such as hepatitis B virus (HBV), cytomegalovirus (CMV) and herpes zoster, need special consideration during treatment. Low-dose oral corticosteroid therapies (eg prednisone 10 mg/day orally for four weeks) may increase the risk of reactivation by up to 10% in hepatitis B surface antigen (HBsAg)-positive individuals while medium-dose corticosteroids (eg prednisone 10–20 mg/day orally) may increase the risk of reverse seroconversion in (HBsAg)-negative

TABLE I: EFFECT OF CORTICOSTEROIDS ON THE IMMUNE SYSTEM				
IMPACT ON CELL NUMBERS	IMPACT ON CELL FUNCTION	IMPACT ON GENE EXPRESSION	IMPACT ON INFLAMMATORY MEDIATORS	IMPACT ON CELL MIGRATION
↓ Cell development – thymocyte apoptosis	↓ Monocyte/ macrophage proinflammatory function	↓ Pro-inflammatory genes	↓ Prostaglandins	↓ Adhesion molecules
↑ Cell loss – leukocyte apoptosis CD4 cell apoptosis	↓ T-cell proliferation	↑ Anti-inflammatory genes	↓ Leukotrienes	
	↓ B-cell proliferation		↓ Cytokines	
			↓ Nitric oxide	

and anti-hepatitis B core (anti-HBc)-positive individuals.[17]

In the setting of SARS-CoV-2 infection, systemic corticosteroid therapy lasting longer than 15 days increased the risk of CMV infection dramatically (odds ratio, 27.1; 95% CI, 3.24–226; p = 0.002) and was associated with increased mortality related to secondary infections.[18] In the context of autoimmune inflammatory rheumatic diseases, both high daily and cumulative glucocorticoid dose were associated with CMV reactivation, leading to tissue-invasive life-threatening diseases such as colitis, vascular thrombosis and pneumonitis.[19]

INCREASED RISK OF HERPES ZOSTER EVENTS

In a large-population cohort, there was a 59% (adjusted hazard ratio 1.59; 95% CI, 1.48–1.71) increased risk of herpes zoster events in new systemic corticosteroid users. This risk increased with higher cumulative doses, with elevated risk appearing in the month after a single prescription and returning to baseline by the third month after dispensing.[20] The same risk has not been observed for inhaled corticosteroids.[21]

EFFECT ON VACCINE RESPONSES

Another area of concern is the effect of OCS on vaccine responses. The impact differs based on the specific immune response elicited by a vaccine, with cellular responses more severely affected than humoral responses. For instance, corticosteroids reduce the responses to the pneumococcal conjugate vaccine, which is a T-cell-dependent vaccine, more than to the pneumococcal polysaccharide vaccine, which is T-cell-independent.[22] The dose and duration also play a role. According to the United States Centre for Disease Control (US CDC), a dose equivalent to ≥ 2 mg/kg of body weight or ≥ 20 mg/day of prednisone or equivalent for persons weighing > 10 kg administered for ≥ 14 consecutive days is sufficiently immunosuppressive to raise concerns about the efficacy and safety of vaccination. The CDC therefore advises that live-virus vaccination should be deferred for at least one month after discontinuation of OCS therapy. Corticosteroids should be restarted four weeks after a live vaccine and two weeks after a non-live vaccine.[23]

EFFECT ON EXPRESSION OF KEY PROTEINS

Owing to the broad base of tissues that may be affected, corticosteroids may alter the expression of key proteins involved in cellular proliferation and protein synthesis (therefore affecting skin health, wound healing and muscle quality); they may also alter calcium homeostasis (precipitating osteoporosis and risk of fractures) and metabolic events (producing hyperglycaemia due to the decreased effectiveness of insulinergic functions), to mention but a few[3,15,24]

EFFECTS OF SHORT-TERM THERAPY

Short courses of OCS therapy are often considered safe for intermittent use, often without sufficient rationale in the clinical decision-making process or without consideration of the risk of potentiating morbidity and mortality.[16] Of concern is the fact that the adverse effect profiles of short-term therapy (40–50 mg/day for five to 30 days) may still parallel those for longer or higher exposure levels.[16] Dose-related morbidity and mortality related to adverse effects have also been observed for patients, with ties to cardio-cerebrovascular, diabetes Type II and osteoporosis risk.[25,26] Patients who have been treated with short-term therapy had a higher incidence of metabolic (diabetes Type II, dyslipidaemia, weight gain) and cardiovascular disorders (myocardial infarction, hypertension, heart failure), cerebrovascular accidents, osteoporosis, ophthalmic disorders (glaucoma, cataracts), pneumonia, and mood disorders compared to those naïve to short-term therapy.[27]

CONCLUSION

Working as they do through non-genomic and genomic pathways to decrease pro-inflammatory mediators and enhance the production of anti-inflammatory molecules, corticosteroids are widely employed in treating various inflammatory and immune-mediated conditions, including asthma. However, they can trigger numerous side effects that diminish patients' quality of life and render them susceptible to additional health complications. Owing to the widespread presence of the glucocorticoid receptor and the diverse mechanisms of corticosteroid action, receptor modulation affects a complex network of physiological processes. Both extended and brief courses of treatment have been associated with immune suppression, metabolic and cardiovascular disorders, stroke, bone loss, eye problems, pneumonia and psychological disturbances, therefore rationalising the increased call to action for systemic corticosteroid stewardship. Consequently, healthcare providers should weigh the potential risks of short- and long-term corticosteroid use, as both may induce pathophysiological changes.

Finally, it should be remembered that '[c]ortisone is the fireman who puts out the fire, it is not the carpenter who rebuilds the damaged house'.[1]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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