Steroids: How Much is Too Much?

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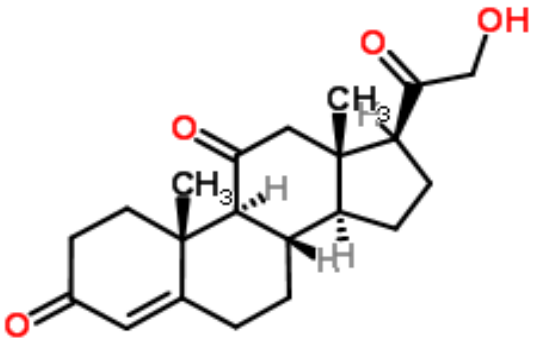

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Purpose & Overview:

The purpose of this presentation is review the use of corticosteroids including their discovery, mechanisms of action, clinical use in systemic lupus erythematosus and rheumatoid arthritis, side effects and potential organ damage with the chronic use.

Objectives:

1. Recognize that corticosteroids have genomic and non-genomic mechanisms of action.
2. List the clinical use of corticosteroids in systemic lupus erythematosus and rheumatoid arthritis.
3. Discuss the potential side effects of the clinical use of corticosteroids.

Biosketch:

Dr.Quiceno is originally from Medellin, Colombia and received his medical degree from CES University in Medellin. He completed his Internal Medicine residency through the William J. Harrington Training Program for Latin America at the Miller school of Medicine at the University of Miami and Rheumatology fellowship at the University of Texas Southwestern Medical Center. He has dedicated his career to medical education and was associate program director in the Internal Medicine residency program at the Texas Health Resources/Presbyterian Hospital of Dallas. After 5 years of private practice he returned to UT Southwestern as faculty in 2012 and since 2015 is the Rheumatic Diseases fellowship program director.

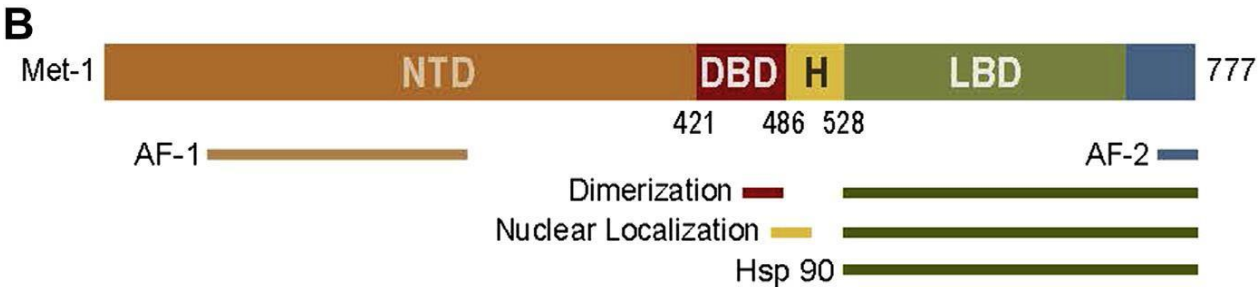
INTRODUCTION

Corticosteroids (CS) are one of the most commonly used medications in modern medicine. Cortisone was the first steroid successfully used clinically by Dr.Philip Hench from Mayo Clinic in 1948 on patients with rheumatoid arthritis after having been developed by Dr.Edward Kendall. They won the Nobel prize in Medicine and Physiology in 1950 that was shared with Dr.Tadeus Riechstein for this discovery. (1, 2) CS play a very important role in the treatment of multiple diseases but their use is limited due to the potential side effects.

MECHANISMS OF ACTION OF CORTICOSTEROIDS

The physiological effect of CS is mediated via the intracellular glucocorticoid receptor (GR) that is a member of the nuclear receptor family of ligand-activated transcription factors. (3) The human GR is located on one locus of chromosome 5q31-32 but differences in the structure and expression of the gene generates diversity in the glucocorticoid signal. (4) The GR has three functional domains: N-terminal transactivation domain (NTD), a central DNA binding domain (DBD), and a C-terminal ligand-binding domain (LBD). (3)

Figure 1. Glucocorticoid receptor



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The NTD contains the transcription activation function (AF1) that activates the target genes. The DBD harbors 2 zinc motifs that bind the target DNA sequences called glucocorticoid response elements (GREs), upregulating (**transactivation**) or downregulating (**transrepression**) the synthesis of proteins that can mediate inflammation. The LBD is known as the hinge region. (3,5)

Genomic Actions of Corticosteroids

Glucocorticoids signal through genomic and nongenomic pathways. The classic genomic actions are mediated via GR. In absence of stimulation, the GR resides in the cytoplasm as part of a large multiprotein complex. The multiprotein maintains the cytoplasmic GR complex in a conformation that favors the high affinity ligand binding. When the GR is activated, it undergoes a conformational change that results in the dissociation of the multiprotein complex and then the GR is transferred to the nucleus. (3)

Once in the nucleus, GR binds to GREs and stimulate the target gene expression by a coordinated recruitment of co-regulatory and chromatin remodeling complexes that influence the activity of the RNA polymerase II and actives gene transcription or repression. (3) These actions can down regulate the synthesis of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-alpha), interleukin 1 (IL-1) and interleukin 6 (IL-6); the majority of the anti-inflammatory effect is mediated by transrepression. These actions also interfere with the function of transcription factors such as NF-kB, activator protein-1(AP-1) and nuclear factor for activated T cells (NF-AT). (3,4,5)

Nongenomic Actions of Glucocorticoids

Nongenomic mechanisms of action are rapid (effects seen within seconds to minutes) because protein synthesis is not required. These effects are mediated through interactions with the membrane bound GR (mGR) that are present in monocytes and B cells of patients with RA. Interactions with the cytoplasmic GR release co-chaperone proteins such as Scr that inhibit phospholipase A2 activity and phosphorylates annexin1 impairing the release of arachidonic acid. (3)

CLINICAL USE OF CORTICOSTEROIDS

Table 1. Corticosteroid dose and relationship with cellular action

Table 1. Current knowledge on the relationship between clinical dosing and cellular actions of glucocorticoids

Terminology*	Clinical application†	Genomic actions (receptor saturation)‡§	Nongenomic actions§	
			Nonspecific	cGCR-mediated
Low dose (≤7.5 mg/day)	Maintenance therapy for many rheumatic diseases	+ (<50%)	–	?
Medium dose (>7.5 to ≤30 mg/day)	Initial treatment for primary chronic rheumatic diseases	++ (>50 to <100%)	(+)	(+)
High dose (>30 to ≤100 mg/day)	Initial treatment for subacute rheumatic diseases	++(+) (almost 100%)	+	+
Very high dose (>100 mg/day)	Initial treatment for acute and/or potentially life-threatening exacerbations of rheumatic diseases	+++ (almost 100%)	++	+(+?)
Pulse therapy (≥250 mg for 1 or a few days)	For particularly severe and/or potentially life-threatening forms of rheumatic diseases	+++ (100%)	+++	+(++?)

* Values represent mg of prednisone equivalent per day. See ref. 9 for further information.
† See ref. 9.
‡ See ref. 10.
§ cGCR = cytosolic glucocorticoid receptor; ? = unknown; – = not relevant; (+) = perhaps relevant, but of minor importance; + = relevant; +(+?) = relevant or perhaps even very relevant; +(++?) = relevant or perhaps even very or most relevant; ++ = very relevant; ++(+) = very relevant to most relevant; +++ = most relevant.

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Corticosteroids in Rheumatoid Arthritis

About 60% of patients with rheumatoid arthritis (RA) are treated continuously with prednisone and besides the genomic and nongenomic mechanisms, steroids in RA have their effect through membrane bound GR (mGR). (5, 6)

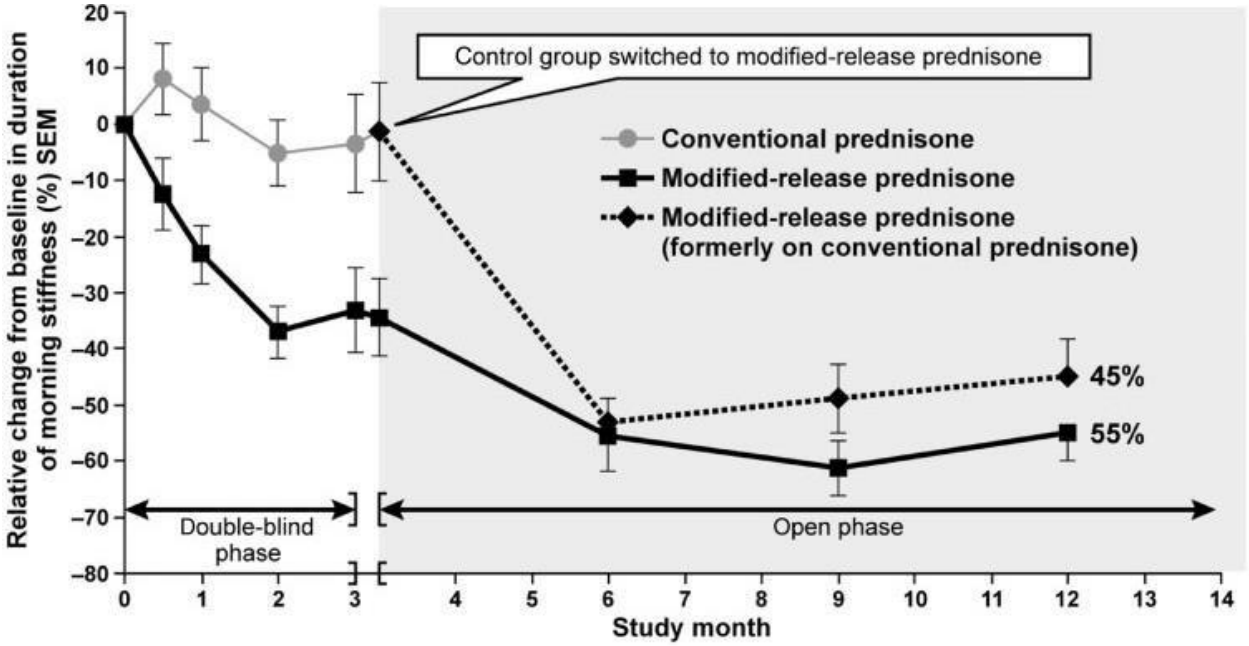
Since the clinical use in 1948 of CS, they have been used in the treatment of RA and have an important role in symptomatic treatment and probably can alter the course of the disease by decreasing the radiographic progression.

Morning Stiffness

Patients who are in remission or with low disease activity, up to 24% still have morning stiffness that lasts more than one hour. (7) In the circadian administration of prednisone in RA (CAPRA) study, it was shown that the addition of 5 mg of modified prednisone (special preparation that released the dose 4 hours after the ingestion), when taken at 10 PM, significantly improved morning stiffness compared with the use of regular prednisone in the morning and patients that were on the regular prednisone improved when crossed over to the modified prednisone regimen. The effect of modified prednisone is associated with the inhibition of IL-6 that is perhaps the main cytokine that mediates morning stiffness in patients with RA. Figure 2 (7,8)

Figure 2.

CAPRA



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Are corticosteroids a disease modifying anti-rheumatic drug?

Despite the wide use of steroids in RA, not all rheumatologists consider steroids as a disease modifying anti-rheumatic drug (DMARD). Svensson, et al studied the effect of adding prednisolone at the start of treatment with a DMARD in patients with early RA and found that the addition of prednisolone decreased the radiographic disease progression and more patients obtained remission compared with patients that only received DMARDs. Table 2. (9)

Table 2.

Change in total Sharp score after 2 years

Prednisolone	No prednisolone	P value
1.8 (**IQR*** 0.5-6.0)	3.5 (**IQR** 0.5-10)	P=0.018

*Interquartile range

Created from data from (9)

In a systematic literature review and expert opinion paper, Dernis et al. did several recommendations for the use of steroids in RA but all were grade D recommendations because the limited number of studies available. (10)

Table 3. Recommendations for the use of corticosteroids in RA

The eight recommendations about the use of glucocorticoids in rheumatoid arthritis, with the extent of agreement among experts.

Recommendations	Agreement among experts % (number)	Grade
In patients with RA, bolus glucocorticoid therapy should be reserved for highly selected situations (such as bridge therapy while waiting for a DMARD to take full effect in a patient who has failed oral glucocorticoid therapy), and patient-related factors should be carefully evaluated	74.4 (n=79)	D
When intraarticular glucocorticoid therapy is used to treat RA, triamcinolone hexacetonide should be preferred over other agents, provided needle placement within the joint cavity can be guaranteed (effusion or image-guided injection)	63.4 (n=80)	D
After an intraarticular injection of triamcinolone hexacetonide used to treat RA, the joint should be rested for about 24 hours	86.2 (n=78)	D
After a triamcinolone hexacetonide injection into the knee of a patient with RA, the joint should be immobilized for about 24 hours	51.3 (n=76)	D
When oral glucocorticoid therapy is given to treat RA, a short half-life agent should be used (prednisone or prednisolone), preferably with a once-daily dosing schedule	75.6 (n=79)	D
In patients with RA who experience severe and long-lasting morning stiffness, a glucocorticoid dose in the evening may be appropriate	80.8 (n=79)	D
When withdrawing long-term glucocorticoid therapy in a patient with RA, the patient and physician should be informed of the risk of adrenal insufficiency	66.3 (N=79)	D
When withdrawing long-term glucocorticoid therapy in a patient with RA, an ACTH stimulation test and/or hydrocortisone administration may be appropriate but are not mandatory	64.4 (n=78)	D

Reproduced from (10)

In conclusion, CS play a very important role in symptomatic treatment of RA and low doses in combination with DMARDs decrease radiographic disease progression and increase the chances of obtaining disease remission.

Corticosteroids in SLE

Corticosteroids were used early on in systemic lupus erythematosus (SLE) after the reports of efficacy in RA and quickly revolutionized the treatment of SLE by rapidly inducing remission but it became clear that they caused significant side effects. CS still remain the cornerstone of the treatment of SLE and up to 88% of the patients are treated with them and often continuously. (11)

Corticosteroids in lupus nephritis

Lupus nephritis occurs in 40% to 60% of adult patients and up to 80% of children with SLE. The highest incidence of SLE and lupus nephritis is in young African-American women. (12)

Boumpas et al. compared pulse methylprednisolone with two different regimens of cyclophosphamide (long and short) and found that patients who received methylprednisolone had a higher risk of doubling the creatinine compared with those that received cyclophosphamide. In this study, CY-L (long regimen) of cyclophosphamide treatment was more effective preserving the renal function. Figure 3(13)

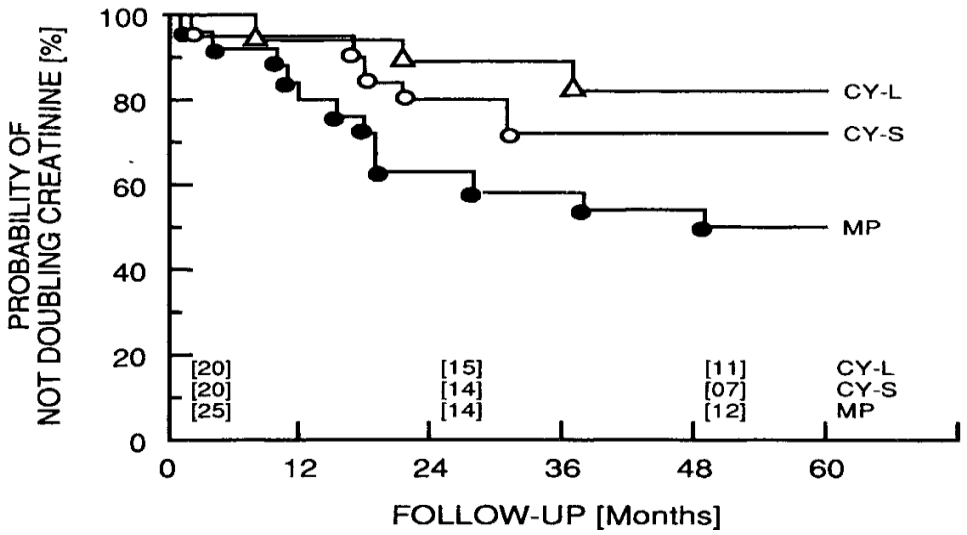

Figure 3 Risk of not-doubling serum creatinine

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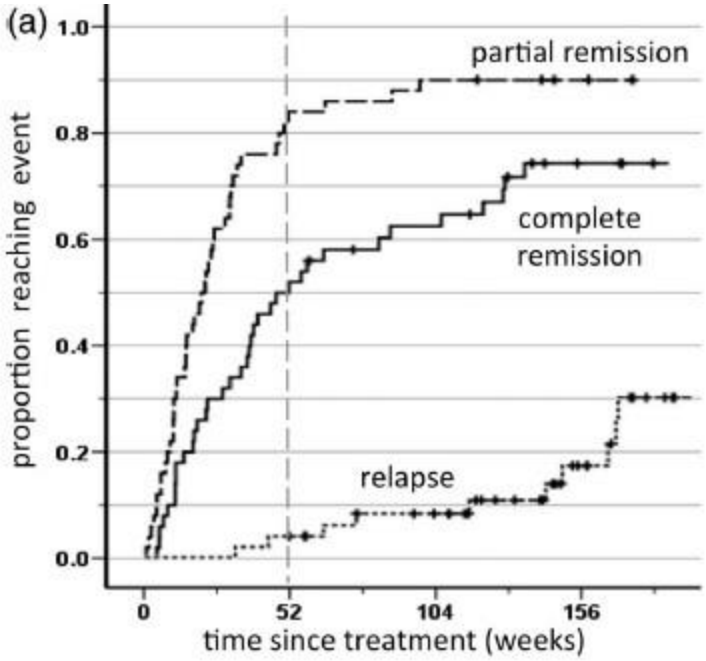
The Rituxilup cohort reported 50 consecutive patients with lupus nephritis class III, IV and V that received rituximab 1000 mg and methylprednisolone 500 mg at days 1 and 15 followed by maintenance therapy with mycophenolate mofetil, 45 patients (90%) achieved partial or complete remission by a median time of 37 weeks without oral steroids, suggesting that patients can obtain remission with lower exposure to CS. Figure 4 (14)

Figure 4. Proportion of patients achieving partial or complete remission



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Corticosteroids in CNS lupus

Central Nervous System (CNS) involvement happens in about 10% of patients with SLE but there are no controlled trials and treatment recommendations are based on expert opinion. High doses or pulse CS are considered the standard of care for patients with acute confusional state, myelitis, refractory seizures and psychosis; other manifestations such as cognitive impairment don’t respond to immunosuppression. (14)

Corticosteroids in other clinical manifestations of SLE

Recommended doses in the treatment of SLE are based on expert opinion because the lack of controlled studies but table 4 summarizes the doses that are considered standard of care.

Table 4.

Traditional recommended dose of CS in SLE

Clinical Manifestation	**Recommended prednisone dose**
Fever and constitutional symptoms	20 to 100 mg/day
Musculoskeletal	20 mg/day
Hematological*	High dose or pulse
Cardiac^	Moderate to high dose
Pulmonary~	Moderate to high dose, pulse for AH

***Immune thrombocytopenic purpura (ITP), autoimmune hemolytic anemia (AIHA)**

^ Pericarditis, myocarditis

~ Pleuritis, alveolar hemorrhage (AH).

Created from data (11)

Complications of the use of corticosteroids

The main complications of CS include: infection, osteoporosis, venous thromboembolism, avascular necrosis, fractures, osteoporosis, diabetes mellitus, hypertension and Cushing's syndrome.

Morbidity is increased early during treatment with CS. In a population based cohort in United States, adults had an increased risk for sepsis, venous thromboembolism and fracture, as early as 30 days after starting treatment. Table 5 (15)

Table 5. Increased risk of complications within 30 days of corticosteroid initiation

Sepsis	**IRR* 5.30**, (95% CI^ 3.8-7.41)
Venous thromboembolism	**IRR 3.33**, (95% CI 2.78-3.99)
Fracture	**IRR 1.87**, (95% CI 1.69-2.07)

*Incidence rate ratio, ^ Confidence interval

Created from data (15)

Patients with rheumatic diseases have an increased risk for infection that is intrinsic to the disease. A population based study in Minnesota found that patients with RA have a higher risk for infection after adjusting for risk factors, such as immunosuppression (16) with a hazard ratio (HR) of 1.83 (95%CI, 1.52-2.21). The risk for hospitalization for pneumonia increases in RA patients and is associated to the dose of prednisone. (17) Table 6.

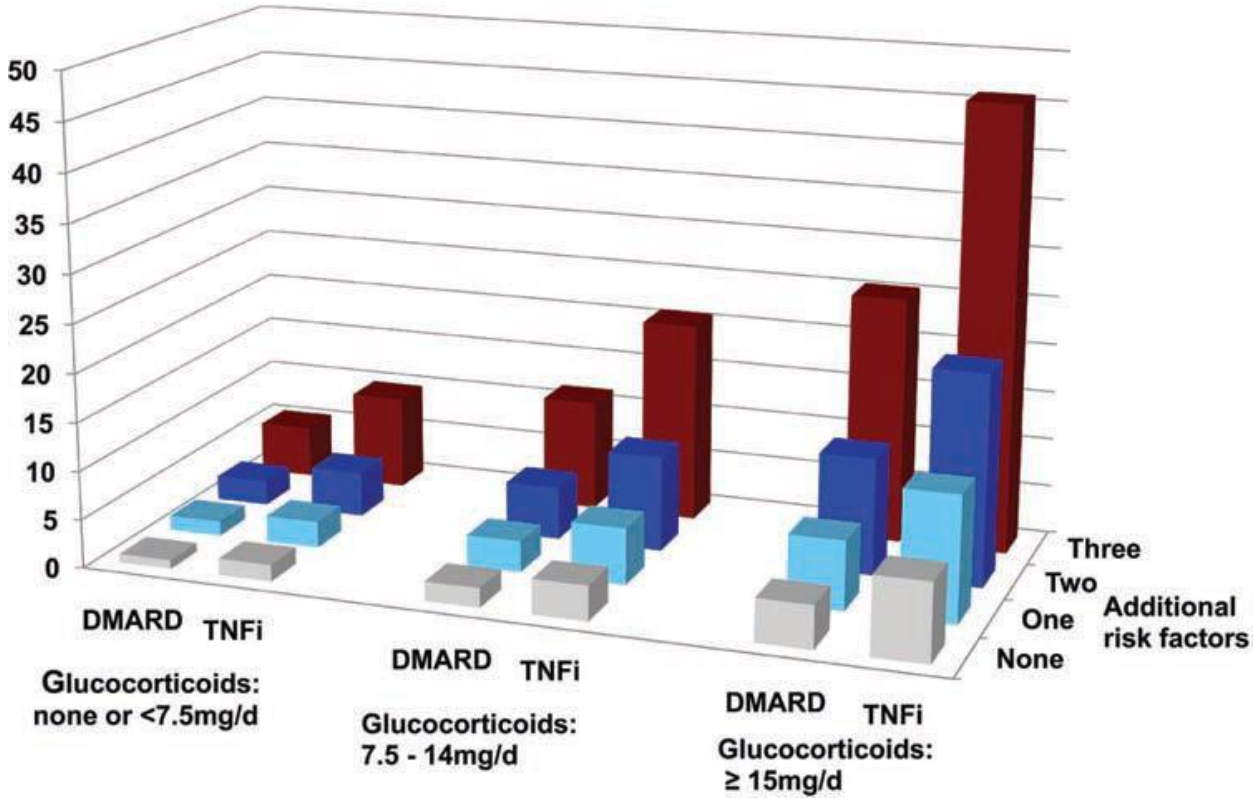
Table 6. Predictors of hospitalization in patients with RA

	Unadjusted			Adjusted†		
Variable	Hazard ratio	*P*	95% CI	Hazard ratio	*P*	95% CI
Prednisone, all dosages	2.3	<0.001	1.9–2.7	1.7	<0.001	1.5–2.1
No prednisone	1.0			1.0		
Prednisone ≤5 mg/day	1.7	<0.001	1.4–2.1	1.4	<0.001	1.1–1.6
Prednisone >5–10 mg/day	2.9	<0.001	2.3–2.7	2.1	<0.001	1.7–2.7
Prednisone >10 mg/day	3.1	<0.001	2.2–4.3	2.3	<0.001	1.6–3.2
Methotrexate	1.0	0.951	0.9–1.2	1.0	0.884	0.8–1.2
Hydroxychloroquine	0.8	0.011	0.6–0.9	0.9	0.331	0.7–1.1
Leflunomide	1.3	0.003	1.1–1.6	1.3	0.036	1.0–1.5
Sulfasalazine	0.6	0.027	0.4–1.0	0.7	0.053	0.4–1.0
Infliximab	1.5	<0.001	1.3–1.7	1.2	0.182	0.9–1.4
Etanercept	0.7	0.013	0.5–0.8	0.8	0.051	0.6–1.0
Adalimumab	1.4	0.257	0.8–2.3	1.1	0.816	0.6–1.8

Reproduced from (17)

Patients with RA that receive treatment with DMARD and biological therapies, such as the TNF Inhibitors etanercept or infliximab, the risk of infection is more dependent on the dose of steroid than on the addition of biological therapy. (18) Figure 5.

Figure 5 Estimated incidence of serious infections in patients treated with DMARD with and without a TNF inhibitor



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Effect of corticosteroid use in developing organ damage in SLE

Prognosis in SLE is established by the severity of the irreversible organ damage. Chronic use of CS is associated with accrual irreversible organ damage. Patients on an average daily dose of > 20 mg/day of CS have an increased risk of accumulating any organ damage compared with patients on average of < 7.5 mg/day. The increased risk is seen in every individual organ such as eye, bone or cardiovascular damage. (19)

Table 7. Any organ damage in lupus by corticosteroid dose

>20 mg/day vs < 7.5 mg/day	HR*=2.514 P< 0.001

***Hazard ratio**

Created from data (19)

Other studies have confirmed these findings, Pego-Reigosa et al. divided a Spanish SLE cohort in 3 clusters: 1. Minimal damage, 2. Musculoskeletal damage and 3. Cardiovascular damage. In patients with cardiovascular damage, there is a 5 fold increase in mortality as compared with the patients with minimal damage. Patients with musculoskeletal damage have a 3 fold increase in mortality. The majority of the musculoskeletal damage was osteoporotic fractures that were attributed to use of CS suggesting a direct role of prednisone in organ damage that increases mortality (20). The University of Toronto Lupus Clinic Cohort also revealed that patients with greater exposure to CS have more accrual organ damage and increased mortality. Table 7. (21)

Table 7. Mortality and accrual organ damage lupus patients glucocorticoid exposed vs non exposed

Variable	Steroid-naive	Steroid-exposed	*P*
No. of patients	86	173	–
Mortality at any time	4 (4.7)	23 (13.3)	0.032
Years from enrollment to death, mean ± SD	12.50 ± 3.82	15.16 ± 7.62	0.505
Deaths within 3 years, no.	0	0	NA
Deaths within 5 years, no.	0	1	0.48
Deaths within 8 years, no.	0	6	0.081
CAD at any time	3 (3.5)	10 (5.8)	0.426
Years from enrollment to CAD, mean ± SD	9.41 ± 4.59	21.55 ± 9.77	0.066
CAD within 3 years, no.	0	0	NA
CAD within 5 years, no.	1	0	0.155
CAD within 8 years, no.	1	0	0.155
SDI increase (any time)	29 (33.7)	110 (63.6)	< 0.001
Age at SDI increase, mean ± SD years	53.0 ± 13.2	42.7 ± 13.7	0.0006
Year from enrollment to 1st SDI increase, mean ± SD	6.33 ± 4.79	6.88 ± 5.64	0.628
SDI increase within 3 years	10 (11.6)	33 (19.1)	0.129
SDI increase within 5 years	12 (14.0)	53 (30.6)	0.004
SDI increase within 8 years	19 (22.1)	73 (42.2)	0.001

* Values are the number (%) unless indicated otherwise. NA = not applicable; CAD = coronary artery disease; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

Reproduced from (21)

Conclusion

Glucocorticoids are very important medications for the treatment of multiple medical conditions but are limited by the potential serious side effects. It is very important to minimize the exposure in patients to decrease morbidity and potential permanent organ damage.

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