The Molecular Mechanism of Corticosteroids for Systemic Lupus Erythematosus Patient’s Treatment and Its Adverse Effects

Ajeng Annamayari, Savira Ekawardhani, Andri Reza Rahmadi, Laniyati Hamijojo, Nur Atik

1Biomedical Sciences Master Program, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia
2Department of Biomedical Sciences, Faculty of Medicine Universitas Pasundan, Bandung, Indonesia
3Department of Biomedical Sciences, Faculty of Medicine Universitas Padjadjaran, Bandung, Indonesia
4Department of Internal Medicine, Faculty of Medicine, Padjadjaran University/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

*E-mail: n.atik@unpad.ac.id

ABSTRACT
Systemic Lupus Erythematosus (SLE) is a complex and multifactorial autoimmune disease characterized by various cellular and molecular aberration resulting in different phenotypes in each individual. SLE occurs worldwide, with the incidence and prevalence varies by country and geographically. Many components of the immune system contribute to the pathomechanism of SLE, where autoimmune plays a significant part. Corticosteroids have been prescribed universally as the mainstay treatment of inflammatory and autoimmune disorders for decades. Corticosteroids have been given in different preparations for treating SLE because of their anti-inflammatory and immunosuppressive activities. While providing clinical benefits to patients significantly, the use of corticosteroid treatment is not without complications and its side effects related to both short and long-term administration. In this context, this review focuses on the molecular mechanism of corticosteroid treatment in SLE patients and its adverse effects.

Keywords: corticosteroids, SLE, molecular mechanism

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Systemic Lupus Erythematosus (SLE) is a complex and multifactorial autoimmune disease characterized by various cellular and molecular aberration resulting in different phenotypes in each individual. SLE occurs worldwide, with the incidence and prevalence varies by country and geographically. Many components of the immune system contribute to the pathomechanism of SLE, where autoimmune plays a significant part. Corticosteroids have been prescribed universally as the mainstay treatment of inflammatory and autoimmune disorders for decades. Corticosteroids have been given in different preparations for treating SLE because of their anti-inflammatory and immunosuppressive activities. While providing clinical benefits to patients significantly, the use of corticosteroid treatment is not without complications and its side effects related to both short and long-term administration. In this context, this review focuses on the molecular mechanism of corticosteroid treatment in SLE patients and its adverse effects.

Keywords: corticosteroids, SLE, molecular mechanism

INTRODUCTION
SLE is a complex, heterogeneous and multifactorial autoimmune disease that very challenging to diagnose and treat as it involves a chronic process of inflammation in multi-organ systems, resulting in variety of clinical phenotypes in each individual (Amissah-Arthur & Gordon, 2010; Bertsias et al., 2012; Cunha & Gilek-Seibert, 2016).

SLE occurs worldwide, with differences by geographically and between countries in the incidence and prevalence rates (Kumar et al., 2009). The SLE incidence rates are about 1 to 10 per 100,000 person-years, while the prevalence rates range from 20–70 per 100,000 person-years in all around the world (Cunha & Gilek-Seibert, 2016; Lim et al., 2014). It is widely known that SLE predilection is more common in women than in men, with a ratio close to 9:1 (Bertsias et al., 2012; Pons-estel et al., 2017); and with significant incidence and prevalence differences in certain ethnic groups, in which non-Caucasians experience higher rates than Caucasians (Amissah-Arthur & Gordon, 2010; Pons-estel et al., 2017; Rees et al., 2017).

The characteristics of SLE are the formation of autoantibodies resulting in the immune complex deposition, complement activation and end-organ damage. This disease was broadly categorized into mild, moderate and severe with autoimmune glomerulonephritis as the most common and life-threatening form of complications. The main focus of therapy is to stop any ongoing systemic inflammation and to induce remission, by controlling immunological activity then followed by less aggressive therapy to consolidate and maintain remission, also reducing the risk of flares (Amissah-Arthur & Gordon, 2010). The molecular mechanisms of corticosteroids in systemic inflammation and immunological activity has been well known.

Corticosteroids are the primary therapy for several autoimmune diseases and other inflammatory disorders, including SLE (Mathias et al., 2017; Petrillo et al., 2017; Shaikh et al., 2012). Although it provides many clinical benefits for patients, the administration of corticosteroids is not without complications, and this relates to the short-term and long-term adverse effects of corticosteroids (Kuhn et al., 2015; Mathias et al., 2017). Thus, the management of SLE is very challenging (Bertolaccini et al., 2018). The survival rate of SLE patients has significantly increased in recent decades, especially due to the improved management and early detection and diagnosis of SLE. However, the mortality rates during the first year after the SLE are also increased due to the activity of the disease, high dose treatment of immunosuppressant such as corticosteroids. It increases patients’ susceptibility to bacterial infections and cardiovascular complications that dominates the first 5 years after the initial diagnosis of SLE (Kuhn et al., 2015). SLE patients are also at risk of being exposed to other adverse effects of corticosteroids related such as hypertension and fluid retention, blurred vision and other emerging side effects such as osteoporosis, avascular necrosis and diabetic-induced steroids (Amissah-Arthur & Gordon, 2010).

The scope of this review is to describe the molecular role of corticosteroid therapy in SLE as well as the long-term adverse effects issues.

MOLECULAR MECHANISM OF CORTICOSTEROIDS FOR SLE TREATMENT AND ITS ADVERSE EFFECTS

Pathomechanism of SLE
SLE etiology includes genetic and environmental factors (Bertsias et al., 2012; Paley et al., 2017). Other certain risk factors, such as female sex, can strongly contribute to the susceptibility of the disease or activate the immune system that causes an inflammatory response, which eventually leads to the development and progression of the disease (Bertsias et al., 2012; Cunha & Gilek-Seibert, 2016).
The patho-mechanism of SLE is complex due to the contribution of various components of the immune system. Which in SLE, autoimmune plays a major part (Cunha & Gilek-Seibert, 2016). The autoimmune reactions in the body induced by the loss of tolerance from the immune system, followed by the consequences of increasing against self-response. The tolerance of the immune system can be central or peripheral. A process in the central lymphoid organs is called central tolerance, where lymphocytes that react to self-molecules will be eliminated by clonal removal and apoptosis in a wide percentage. Some cells that have the ability to self-recognize then diverted to compartments with the regulatory function. Peripheral tolerance can occur when there is mature lymphocytes induced by self-antigens in peripheral tissues and in secondary lymphoid organs. When the selective mechanism of T and B cells recognition for antigens fail, it can be activated by self-antigens, which promote autoimmunity (Bluestone, 2011; Trombetta et al., 2017). It will lead to the production of auto-antibodies, eventually form an immune complex that circulates and deposit in tissues causing organ damaged (Choi et al., 2012; Cunha & Gilek-Seibert, 2016; Trombetta et al., 2017). (Figure 1)

Autoimmunity is also related to underlining of cytokine and chemokines pathways that trigger and regulate the immune response, both innate or adaptive type, along with the hormonal and also genetic influences on T and B cells on the immune system (Benagiano et al., 2019).

Self-tolerance breakdown plays a vital role in the development and occurrence of SLE. SLE is primarily caused by both innate and adaptive immune response to autoantigens, which induce the production of autoantibodies then forming an immune complex deposition in tissues that leads to the accumulation of neutrophils, monocytes, lymphocytes that reactive to autoantigens and complement activations (Kaul et al., 2016; Ohl & Tenbrock, 2011; Pan, et al., 2019; Tsokos et al., 2016).

### Role of Corticosteroids in SLE

Hormones in general, specifically steroid hormones, have an essential role in the physiology and pathology of the immune system, especially adaptive immunity. Corticosteroids are hormone mediators that produced by the adrenal cortex and further categorized into Glucocorticoids (GCs), mineralocorticoids and androgenic sex hormones (Benagiano et al., 2019; Ramamoorthy & Cidlowski, 2016; Van Staa et al., 2000).

Cortisol, the most important human GCs, is a natural and potent anti-inflammatory molecule, synthesized in the cortex of the adrenal gland and then circulated into the body after certain physical and psychological stimuli. The corticosteroid synthesis through the HPA axis activated mostly by the adequate response to stress, pain, and hypoglycemia. The anterior pituitary gland regulates the production of cortisol by the presence of ACTH activity (Trombetta et al., 2017).

The level of cortisol in the circulation follows the circadian rhythm, where cortisol levels will reach its peak in the morning and have their lowest level in the late evening. Cortisol influences the activity and survival of the immune cells, and also modulate several pro-inflammatory cytokines in circulation such as IL-2, IL-6, TNF-α, and IFN-γ (Trombetta et al., 2017). In T cells, cortisol suppresses the function of its receptor through the membrane-bound receptors. Cortisol also works by binding to the GC receptor on mitochondria, reduce their function, eventually leads to cell death (Suarez et al., 2006; Trombetta et al., 2017).

### Molecular mechanism of corticosteroid as SLE Treatment

Corticosteroids have been given for many decades as the treatment of SLE within different preparations and have been central for its role because of their activities. In short-term administration, corticosteroids work as anti-inflammatory agents, while in long-term it will effect as immunosuppressive (Trombetta et al., 2017).

Neuroendocrine systems play a role in the regulation of balancing pro and anti-inflammatory functions in the immune system. These activities regulated by corticosteroids and then control the neuroendocrine system by releasing cytokines that will leads to the increase of steroids production (Trombetta et al., 2017).

Cytokines that produced by immune cells, mainly by T cell, are mediators that involved and have important parts in the activation, differentiation and maturation of various types of immune cells (Grondal et al., 2000; Lai & Yap, 2010). Cytokines can play different roles as inhibitory or excitatory depending on the T cell subgroups. In SLE, there is another important issue of the imbalance between Th1/Th2 cytokines, a paradoxical data about the domination between Th1 or Th2 response. Recent studies bring up the role of Th1 response in pathomechanism of

![Figure 1: Pathomechanism of Systemic Lupus Erythematosus.](image-url)
SLE, yet there is an obvious rise of Th2 in SLE (Tahernia et al., 2017). These cytokines related to SLE from Th1 include IL-12, IFN-α, and TNF-α. While IL-4, IL-6, and IL-10 are from Th2. In addition to that, some other innate immune cytokines such as B cell activating factor (BAFF) and proliferation inducing ligand (APRIL) derived from TNF family, that produced by antigen presenting cells (APC) are also important in the pathomechanism of SLE through the B cells proliferation. Although in SLE, BAFF/APRIL role is not well understood, yet these cytokines level found increases in the serum of SLE patients (Davis et al., 2011; Tahernia et al., 2017; Wong et al., 2000; Zharkova et al., 2017).

GCs have an influence on almost all cell types and especially in immune cells, GCs have been shown to have potent immunosuppressive and anti-inflammatory activities (Coutinho & Chapman, 2011; Liberman et al., 2018). In low concentrations, GCs could activate macrophages through phagocytosis, adhesion, chemotaxis, and production of cytokines, while in high concentrations, GCs have an immunosuppressive role by reducing the production of cytokines, chemokines, number of basophils and histamine production (Figure 2) (Trombetta et al., 2017).

**Figure 2**: Molecular Mechanism of Corticosteroid (CS) in SLE.

SLE is caused by an autoimmune reaction, where there is an inappropriate immune response, either innate or adaptive, to the nucleic acid containing self-antigens. This will leads to form the pathogenic autoantibodies production, where these autoantibodies along with inflammatory cytokines, will cause tissue injury in response to the deposits of immune complexes. Dendritic cells (DC), the antigen presenting cells, play as the key role to the activation of adaptive immune cells, which then contribute to the production of inflammatory cytokines that will activate and change B cell into plasma cell that release autoantibodies. CS act as immunosuppressive upon almost all types of immune cells.

In chronic exposure to GCs, especially in high doses, will affect B cells, resulting in a reduction of cell numbers in lymph nodes and spleen, also the reduction of cell progenitor proliferation, decreases of IgG production and circulating BAFF. Moreover, GCs exposure to DCs will reduce the maturation and ability of DCs to activate the T cells, resulting in decreased proliferation of T Cells and the production of IFN (Figure 2) (Trombetta et al., 2017).

**The Adverse effect of corticosteroid treatments in SLE patients**

The adverse effects of corticosteroids may vary on the amount of dose, duration of treatment, the administration routes, the individual drug bioavailability, and also the mechanism of action of individual corticosteroids (Yasir & Sonthalia, 2019). All of the study types regarding the adverse effect of corticosteroid in SLE are presented in Table 1.

**Skeletal.** The common cause of secondary osteoporosis is the use of corticosteroid (Alan & Alan, 2018; Stojan & Petri, 2017). Fractures are one of the most adverse effects that frequently reported due to the rapid bone loss that could occur up to 12% of SLE patients during the first six months to one year use of the corticosteroid treatment. There is a greater risk for vertebral fractures than other fractures sites elsewhere in patients with the use of corticosteroid, and this risk is three times higher than in SLE patients without the use of corticosteroids as main treatment (Stojan & Petri, 2017).

**Cardiovascular.** The use of corticosteroids in SLE has been related with atherosclerosis (Maggard & Petri, 2012). There are two mechanisms can explained this cardiovascular side effects, a direct influence on the heart and vasculature functions and also the increase of cardiovascular risk factors (Alan & Alan, 2018; Stojan & Petri, 2017).

**Eye.** Corticosteroid effects on the ophthalmic system depend on the route of administrations (Poetker & Reh, 2010). The high incidence of glaucoma in SLE is often associated with the administration of systemic...
corticosteroids. The main mechanism of increased intraocular pressure during SLE treatment is due to functional and morphological changes in the trabecular meshwork that induced by corticosteroids (Alan & Alan, 2018). Posterior subcapsular cataracts are also associated with systemic corticosteroids (Carnahan & Goldstein, 2000). The more potent corticosteroids, such as betamethasone or dexamethasone, both given topically and systemically, the higher the risk of cataracts and glaucoma compared to administering less potent steroids such as prednisolone (Stojan & Petri, 2017).

<table>
<thead>
<tr>
<th>Affects to</th>
<th>Adverse effects</th>
<th>References</th>
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<tbody>
<tr>
<td>Cardiovascular</td>
<td>Increase blood pressure, dyslipidemia, thrombosis and vasculitis that could lead to myocardial infarction and cerebrovascular disease</td>
<td>(Alan &amp; Alan, 2018; Magder &amp; Petri, 2012; Poetker &amp; Reh, 2010; Schäcke et al., 2017)</td>
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<tr>
<td>Gastrointestinal</td>
<td>Peptic ulcer, GI bleeding, pancreatitis</td>
<td>(Alan &amp; Alan, 2018; Poetker &amp; Reh, 2010; Schäcke et al., 2002)</td>
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<td>Metabolism, endocrine system</td>
<td>Adrenal suppression, blood pressure changes, water retention, increase in blood sugar level, hypogonadism,</td>
<td>(Alan &amp; Alan, 2018; Poetker &amp; Reh, 2010; Schäcke et al., 2002)</td>
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<tr>
<td>Immune system</td>
<td>Bacterial, fungal and viral infections</td>
<td>(Alan &amp; Alan, 2018; Lionakis &amp; Kontoyiannis, 2003; Poetker &amp; Reh, 2010; Schäcke et al., 2002; Stojan &amp; Petri, 2017)</td>
</tr>
<tr>
<td>Eye</td>
<td>Cataract, glaucoma</td>
<td>(Alan &amp; Alan, 2018; Carnahan &amp; Goldstein, 2000; Poetker &amp; Reh, 2010; Schäcke et al., 2002; Stojan &amp; Petri, 2017)</td>
</tr>
<tr>
<td>CNS - psychiatric</td>
<td>Steroid psychoses as mood, behavior, memory and cognition disturbances, cerebral atrophy due to steroid dependence</td>
<td>(Alan &amp; Alan, 2018; Poetker &amp; Reh, 2010; Schäcke et al., 2002; Stojan &amp; Petri, 2017; Warrington &amp; Bostwick, 2006)</td>
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<tr>
<td>Skin</td>
<td>Dermal thinning, steroid acne, striae, ecchymosis, delayed of wound healing, delayed reepithelization, decrease fibroblast response, the slow proliferation of capillary, collagen synthesis inhibition</td>
<td>(Alan &amp; Alan, 2018; Poetker &amp; Reh, 2010; Schäcke et al., 2002)</td>
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<tr>
<td>Skeletal system</td>
<td>Decrease bone density, avascular necrosis, muscle atrophy/myopathy</td>
<td>(Alan &amp; Alan, 2018; Poetker &amp; Reh, 2010; Schäcke et al., 2002; Stojan &amp; Petri, 2017)</td>
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<tr>
<td>Morphological</td>
<td>Moon face, buffalo hump, truncal obesity, cushingoid changes</td>
<td>(Permana et al., 2019; Poetker &amp; Reh, 2010)</td>
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**CNS-Psychiatric.** Corticosteroid-induced psychosis occurs in nearly 5% of SLE patients. Corticosteroids can cause psychiatric disorders as well as cognitive disorders. Cognitive deficit such as memory disturbances may appear as early as four days after the start of steroid treatment. And the side effects that arise seem to be dose-dependent related and reversibility of the cessation of the treatments (Poetker & Reh, 2010; Warrington & Bostwick, 2006). Low levels of serum creatinine and albumin, a history of anxiety disorders, and psychiatric disorders in the family can be the predictive factors for corticosteroid-induced psychosis (Stojan & Petri, 2017).

**Immunity.** There are multiple effects of corticosteroids such as immunosuppressive and anti-inflammatory effects that tend to cause infections in SLE patients, where the use of corticosteroids can increase the risk of infection such as bacteria, fungi, and virus, as well as the risk of reactivation from tuberculosis infection (Lionakis & Kontoyiannis, 2003). The risk of this infection can also be associated with the duration of treatment and the amount of dosage use of corticosteroid (Alan & Alan, 2018; Stojan & Petri, 2017).

**CONCLUSIONS**

The use of corticosteroid for SLE treatment is inevitable, based on its molecular mechanisms that can affect a variety of cytokines that can contribute to organ damaged. Although the total care for SLE patients improved, the risk of complications and comorbidities rise, due to the development of the disease or the adverse effects of corticosteroid treatment. Toxicity associated with prolonged use of corticosteroid is the increased morbidity...
and mortality. Hence, the use of corticosteroid should be wisely considered.

ACKNOWLEDGEMENT
This work was supported by grant from Ministry of Research, Technology and Higher Education of the Republic of Indonesia to Nur Atik.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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