RESEARCH ARTICLE

Dexamethasone Mechanism in Inflammatory Immune Mediated Disease and its Application in Treating 2019 Coronavirus Disease (COVID-19)

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Abbreviation:
DEX, dexamethasone; GC, glucocorticoid, HPA axis, hypothalamic pituitary adrenal axis; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; COX-2,cyclooxygenase; NF-κB, nuclear factor kappa; TNF-α, tumor necrosis factor-alpha; ARDS, acute respiratory distress syndrome; ALI, acute lung injury; COPD, chronic obtrusive pulmonary disease; CoV, coronavirus; SARS-CoV-2, sever acute respiratory syndrome coronavirus 2; MAPK, Mitogen-Activated Protein Kinase; MKKK6, MAPK Kinase 6; UTR, untranslated region; GAPDH, Glyceraldehyde 3-phosphate dehydrogenase; CF, cystic fibrosis; MP, methylprednisolone; ALL, acute lymphoblastic leukemia; MM, multiple myeloma; CINV, chemotherapy induced nausea and vomiting; BCVA, best corrected visual acuity.

Abstract

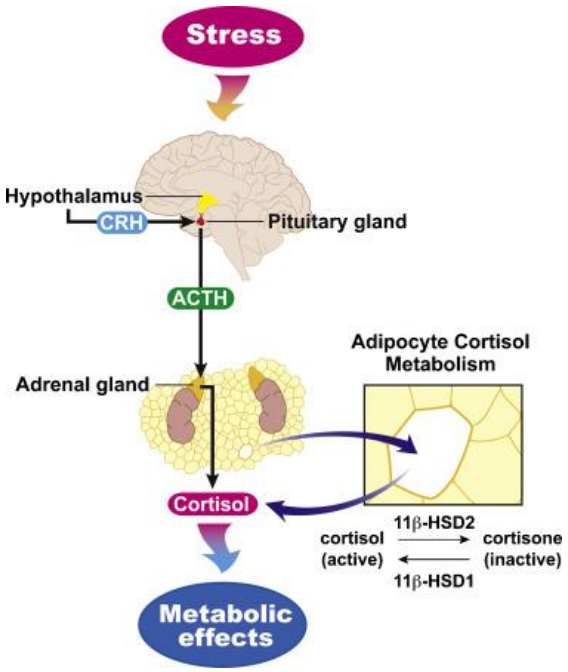
Since the very first medical use of dexamethasone (DEX) in 1958, this glucocorticoid (GC) has been widely used in various clinical applications. Compared to other GCs, DEX is highly potent and comes in multiple formulations for ease of local and systemic administrations. Recently, DEX has a new application for treating COVID-19 patients. DEX mainly inhibits expressions of inflammatory proteins and transcription factors necessarily for cell proliferation. DEX can both upregulate and downregulate expressions of the genes that facilitates anti-inflammatory effects and immunosuppression. Key proteins involved in DEX pathways are NF-κB, AP-1, COX-2, and annexin A1. When used appropriately, DEX can minimize inflammatory pain and damage but it can also delay patient recovery by immunosuppression. Due to this duality, DEX should be used with caution for treatment considerations. Long-term systemic use could lead to debilitating adverse reactions and firm recommendations should be established in treating both acute and chronic disease with DEX.

Keyword: Dexamethasone; Inflammation; Immunosuppression; COVID-19

1. Introduction

As the spread of COVID-19 continues, healthcare providers are taking supportive measures and using existing drugs to help patients' recovery. Some of the existing drugs that are being clinically tested are dexamethasone (DEX),[1-9] hydroxychloroquine,[10-17] azithromycin,[18-27] and toclizumab.[28-34] Among these options, use of DEX is highlighted due to its key indication for Acute Respiratory Disease Syndrome (ARDS). According to World Health Organization's preliminary report based on RECOVERY Trial, patients on ventilators treated with low dose DEX had a decrease in mortality by one third.[1] From this preliminary result, interest in use of DEX has resurfaced.

DEX is classified as a glucocorticoid (GC), which is a synthetic form of cortisol. Cortisol is released upon activation of the hypothalamic-pituitary-adrenal axis (HPA axis, **Fig 1**). When stress induces the hypothalamus, it release the corticotropin-releasing hormone (CRH). CRH then activates the pituitary gland which then releases the adrenocorticotropic hormone (ACTH). Lastly ACTH activates the adrenal cortex to release cortisol. GCs have been used for systemic autoimmune disease, malignancy, dermatosis, chronic lung disease, leukemia, and chemotherapy induced nausea and vomiting.[35] Extended use of glucocorticoids leads to suppression of the HPA axis. For this, GCs need to be tapered off to prevent withdrawals.[36]



CRH: corticotropin-releasing hormone; ACTH: adrenocorticotropic hormone; 11*β-H*SBD1: 11β-hydroxysteroid dehydrogenase type 1; 11*β-H*SBD2: 11β-hydroxysteroid dehydrogenase type 2

Fig. 1. Stress induced HPA Axis. Stress activated hypothalamus release CRH to activated pituitary gland to further release ACTH. ACTH then induce adrenal cortex to release cortisol to carryout various metabolic effects. Cortisol is an active form and its inactive form is cortisone. 11*β-H*SBD1 activates cortisol and 11*β-H*SBD2 deactivates cortisone.[37]

Over the years, glucocorticoid structure has been modified to increase anti-inflammatory potency and minimize adverse reactions, eventually leading to the synthesis of DEX. The addition of a double bond between C_1=C_2 in cortisol led to prednisone **(Fig. 2)**. This allowed 4-5 times greater anti-inflammatory effect than natural hormone and reduced sodium retention activity. The addition of a fluorine at C_9 position increased the anti-inflammatory potency but also increased fluid retention. Introduction of a methyl group at C_{16}, yielding DEX, further increased duration of action and the potency by 25-30 folds. **Table 1** compares relative potency, sodium retaining potency, and half-life of glucocorticoids. Among the list, DEX has the highest potency, with longest half-life of 36-54 hours, and lowest sodium retaining activity.[35, 38, 39] The duration of action is not proportionally related to its effect. This could be due to its nuclear mechanism and regulating gene expressions. As a result, even after DEX is excreted its therapeutic effect may persist; thus measuring duration of action is usually based on suppression of HPA axis.[36]

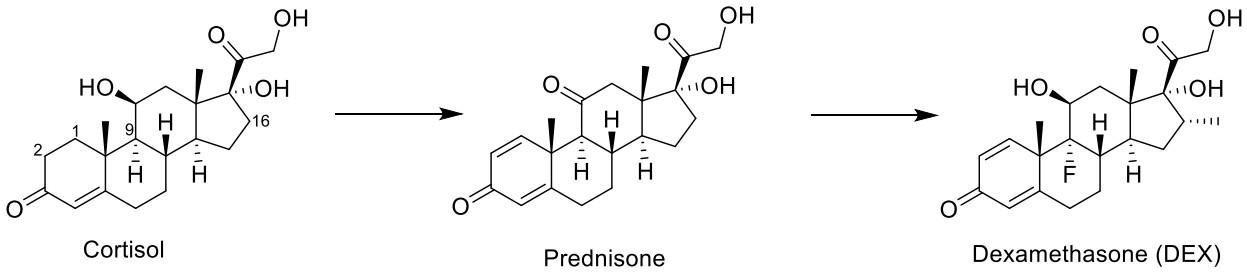


Fig. 2. Order of structures modification to synthesizing DEX. Addition of a double bond in cortisol to C_1=C_2 led to prednisone. Addition of F to C_9 and a methyl group to C_{16} resulted DEX.

Table 1
GCs Common Side Effects[36]

Hypothalamic-pituitary-adrenal axis suppression
Physical appearance changes: moon facies, buffalo hump, central trunk obesity
Growth suppression
Hirsutism
Acne
Insomnia
Increased appetite
Hyperglycemia
Muscle wasting
Reduced bone mineral density and osteoporosis
Increased bruisability
Atrophy of skin
Immunosuppression
Cataracts
Glaucoma
Weight gain
Psychiatric disturbances

Due to its high potency, various adverse reactions can occur with systemic, long-term use of DEX. Although DEX has low mineralocorticoid activities, side effects are similar to other GCs (**Table 2**). Some common side effects of DEX are hypertension, insomnia, osteoporosis, growth retardation, Cushing's syndrome, immunosuppression, weight gain, and muscle atrophy. While some of these side effects can be helpful, such as immunosuppression for transplant and cancer patients, most of are harmful.[35, 36]

Table 2: Corticosteroids Comparison Chart[39]

	Equivalent Glucocorticoid dose (mg)	Potency relative to hydrocortisone		Half-life Duration of action (hours)
		Anti-inflammatory	Mineralocorticoid	
Glucocorticoids				
Short Acting				
Hydrocortisone*	20	1	1	8-12
Cortisone acetate	25	0.8	0.8	8-12
Intermediate Acting				
Prednisone	5	4	0.8	12-36
Prednisolone	5	4	0.8	12-36
Methylprednisolone*	4	5	0.5	12-36
Long Acting				
Dexamethasone*	0.75	30	0	36-54
Mineralocorticoid				
Fludrocortisone	0	15	150	24-36

*These medications are also available to intravenous administration. Doses of intravenous medications are not equivalent to oral medications.

DEX is a low-molecular weight (MW 392.5 g/mol) drug with a log P value of 1.8.[40] Oral availability of DEX is between 70%-78% and it is also available in IV injectable solutions.[41] DEX is predominantly metabolized in the liver through CYP3A4 enzymes forming 6β-hydroxydexamethasone (**Figure 3**). DEX also undergoes Phase 1 metabolism via the CYP17 family (17, 20 lyase) in the kidney, cleaving the sidechain to form 9α-fluoro-androsta-1,4-diene-l l β-hydroxy-16α-methyl-3,17-dione (9αF-A). 9αF-A can then be further metabolized to its 6β-hydroxylated product.[42,43] Ultimately, DEX and its metabolites are predominantly excreted in its glucuronide forms. Some CYP3A4 inducers such as phenobarbital, rifampin and inhibitors such as ketoconazole can effect DEX levels.[36] Additional drug interactions are listed in **Table 3.**

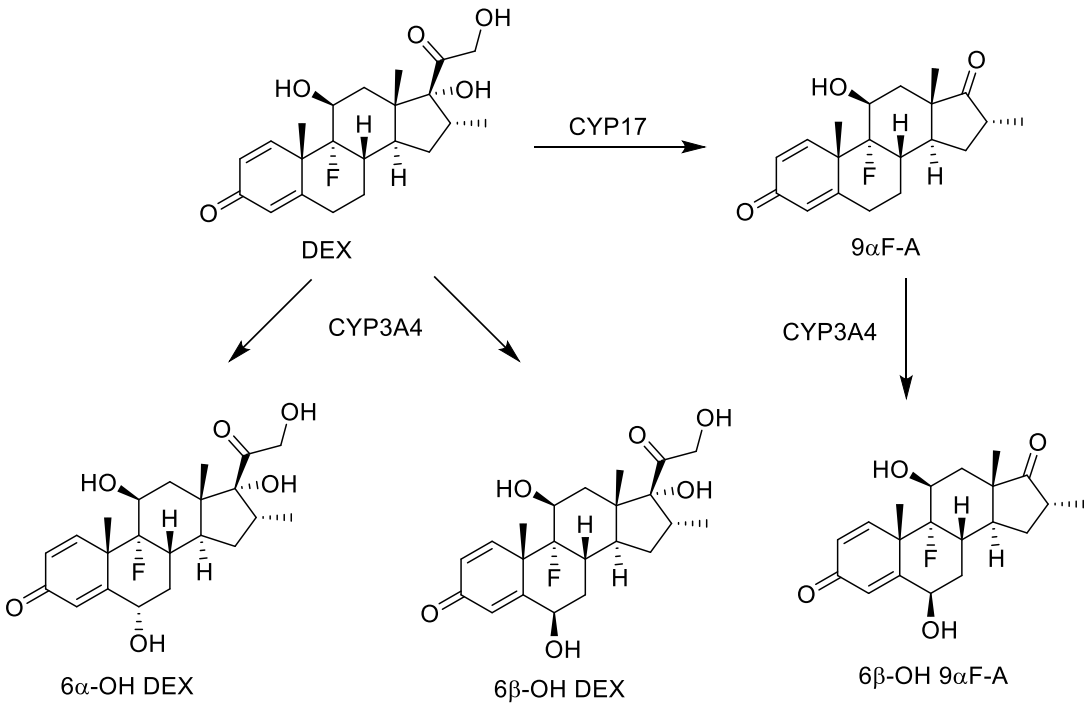


Fig.3. Phase 1 metabolism of DEX by CYP17 and CYP3A4 [42]

Table 3: Glucocorticoids Drug Interactions[36]

Ace inhibitors	**Antagonize hypotensive action of ACE-inhibitors**
Amphotericin B	Increased risk of hypokalemia
Antidiabetic agents	Antagonism of blood glucose lowering; hyperglycemia
Antihypertensives	Antagonism of hypotensive effects
Carbamazepine	Increased metabolism of corticosteroid
Cobicistat and ritonavir	Increased concentration of corticosteroid
Estrogens	Increased concentration of corticosteroid
Grapefruit juice	Increased concentration of corticosteroid
Inhaled β_2 agonist	Increased risk of hypokalemia
Ketoconazole and itraconazole	Increased concentration of corticosteroid
NSAIDs, including salicylates	Increased risk for gastrointestinal bleeding
Phenobarbital	Increased metabolism of corticosteroids
Rifampin	Increased metabolism of corticosteroids
Vaccines	Reduced effect of vaccines
Warfarin	Increased or decreased effect of warfarin
Cyclosporine	Increased concentration of cyclosporine

ACE: angiotensin-converting enzyme
NSAID: Nonsteroidal anti-inflammatory drug

DEX affects different pathways indicated for each disease state. This also suggest the potential to various adverse events while treating a disease state. With vigilant use, DEX's influence on various pathways broadens the scope of its application. The following sections will explore different pathophysiological uses associated with DEX and its mechanisms of action for the treatment of various disease, including COVID-19.

2. ARDS & Anti-Inflammatory Effects of DEX

2.1. Pathogenesis of ARDS

The pathology of Acute Respiratory Distress Syndrome (ARDS) was first suggested in 1977. ARDS is a profound inflammatory action that induces respiratory failure. ARDS presents with a combination of dyspnea, hypoxemia, rapid breathing, and hypotension. It is also associated with extra-pulmonary organ failures that can worsen the patient's overall symptoms. Some common disorders associated with ARDS are pneumonia, sepsis, pancreatitis, drug reactions, and trauma. In 2005 approximately 200,000 patients presented with acute lung injury (ALI) and ARDS with a 40% mortality rate.[44-46] Currently, ARDS mortality rate ranges from 27%-45% depending on its severity.[14]

The pathogenesis of ARDS **(Fig. 4)** involves increased permeability of fluid accompanied with an increase in white blood cells, inflammatory mediators, and cytokines. Another mechanism involves impaired function to resolve edema and infiltration of inflammatory cells. Part of the impaired function involves accumulation of fibroblast and excessive collagen synthesis leading to scar formation. The initial stage in the alveoli presents with edema, clusters of neutrophils, and macrophages. As the stage progresses, repairs begin with new alveolar cells and decreased edema. In this process, infiltration of fibroblasts may then occur. The last phase consist of a decrease in neutrophil with an increase in macrophages and fibrosis. Although most cases are resolved without fibrosis, it may continue with constant attempts to repair alveolar epithelial cells.[44,48,49]

While the damages from ARDS largely involves endothelial and epithelial injuries, ventilator-associated lung injury is a significant part of its pathogenesis. ARDS patients are often supported with positive pressure ventilation. However, previous common practices with high tidal volume increased airway pressure causing more inflammation and mechanical lung injuries. More evidence supported this cause when comparing the previous strategy to low tidal volume and air pressure.[50,51] Patients on ventilators with low tidal volume and air pressure had lower plasma levels of inflammatory cells and cytokines.[52,53] With this new ventilation strategy in 2006, mortality of ALI decreased by 15% compare to that of 2007's. These findings highlights significance of ventilator strategy that can contribute to treating ARDS.[44,54]

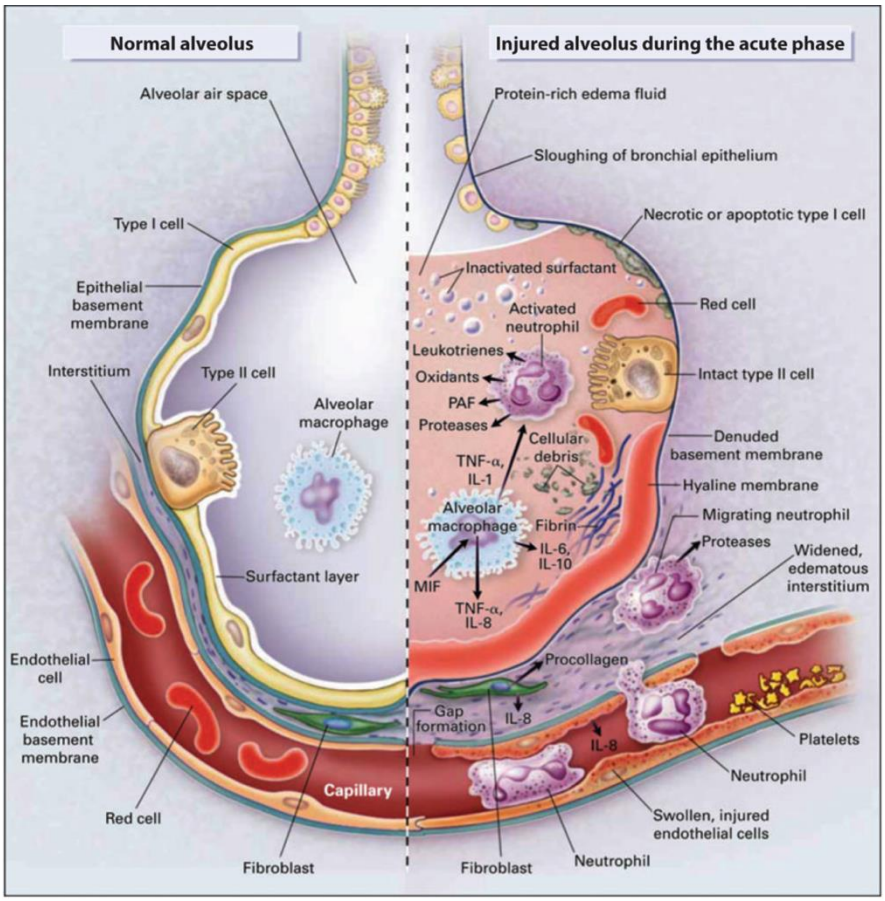


Fig. 4. Normal alveolus versus acutely injured alveolus[11]

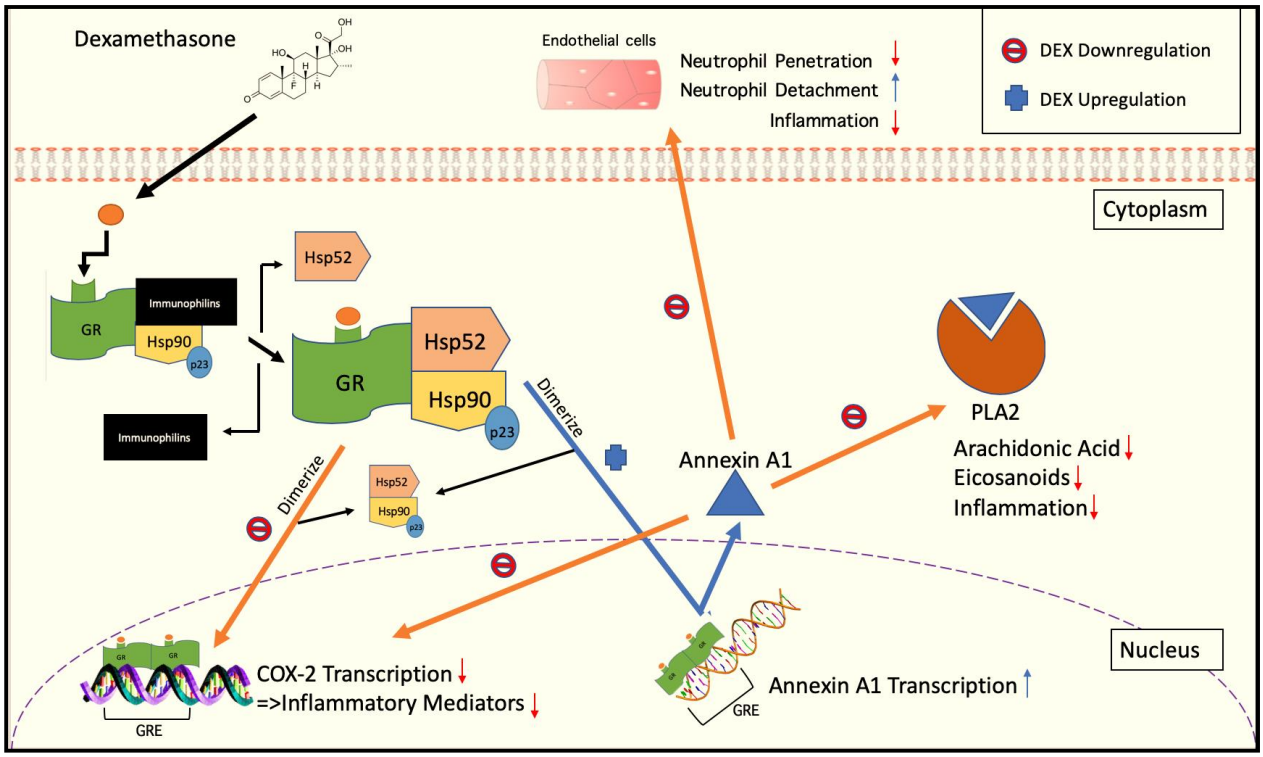
2.2. DEX Anti-Inflammatory Pathways

Since the pathogenesis of ARDS involves inflammation, DEX's anti-inflammatory mechanism suggest its use as a treatment option. DEX's anti-inflammatory mechanism is mainly divided into two pathways; A) inhibiting regulation of inflammatory gene expression and B) upregulating gene expressions that ultimately inhibits inflammatory gene expression. Initially, DEX enters the cell and can bind to its cytosolic glucocorticoid receptor **(Fig. 5)**. As the receptor's chaperon protein is cleaved it forms a complex with Hsp52. This complex translocates to the nucleus which then forms a dimer ready to control gene expression. Both pathways involve intracellular and nuclear action suggesting delayed response through gene regulation.[55-57]

DEX inhibits the gene expressions of both cyclooxygenase 2 (COX-2) and inducible nitric oxide synthase (iNOS aka NOS II). COX-2 enzymes covert arachidonic acids to inflammatory mediators such as prostaglandins.[56,58] DEX inhibits the expression of COX-2, ultimately decreasing inflammatory mediators. Conversely, NOS II is inhibited in more indirect ways. While interleukin-B (IL-1) is involved directly inducing NOS II expression, IL-1 indirectly activates nuclear factor-kappa B (NF-κB), which then induces NOS II. Ultimately, NOS II is activated to produce nitric oxide (NO).[59] NO acts as a pro-inflammatory mediator when overly produced in response to

cytokines.[58] In addition, NF-κB itself regulates expressions of pro-inflammatory cytokines and proliferation of immune cells, including inflammatory T cells.[60] By inhibiting expression of COX-2 and NF-κB mediated inflammatory genes transcription, DEX decreases inflammation.

Furthermore, DEX upregulates the expression of annexin A1 (lipocortin I), which is involved in numerous anti-inflammatory actions. Annexin A1 directly inhibits cytosolic phospholipase A2 (PLA2). PLA2 is responsible for synthesizing arachidonic acid, which is necessary to catabolize inflammatory mediators.[56,57,61] Additionally, annexin-A1 also inhibits regulation of COX-2 gene expression, which ultimately decreases inflammatory cytokines.[62] In addition to eicosanoid signaling pathways, annexin A1 also prevents neutrophil transmigration and adhesion to endothelial cells (**Fig. 6**).[57] This mechanical prevention of neutrophil's responsiveness further inhibits the inflammatory cascade. Overall, DEX simultaneously upregulates and downregulates gene expression that fundamentally decreases inflammation.



COX-2: Cyclooxygenase 2; PLA2: Phospholipase A2; GR: Glucocorticoid receptor; GRE: Gene response element

Fig. 5. DEX Anti-Inflammatory Pathways. DEX upregulates expressions of annexin A1 and downregulates COX-2 transcription, ultimately decreasing inflammatory mediators. annexin A1 inhibits PLA2 and neutrophil penetration to endothelial cells decreasing inflammation [55 modified]

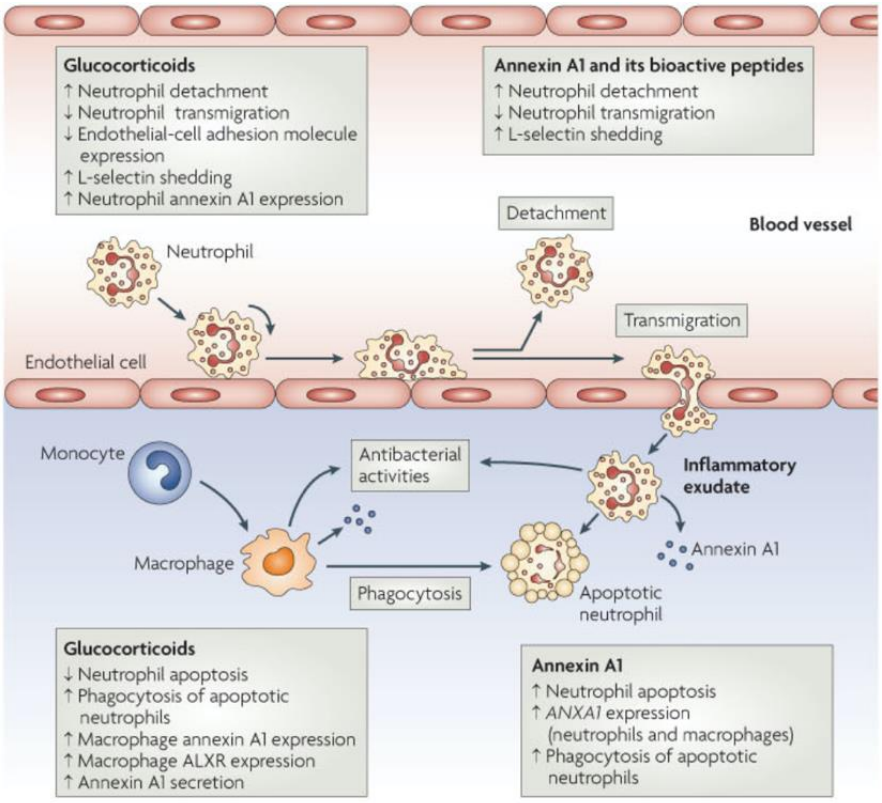


Fig. 6. Roles of annexin-A1 in neutrophil detachment and transmigration[57]

2.3. Treating ALI/ARDS with Dexamethasone

Previously, other drugs such as heparin, ketoconazole, and ibuprofen have been studied in treating ARDS but didn't provide positive results in improving patient outcomes. Other corticosteroids such as methylprednisolone were tested for treating ARDS patients but mortality differences were not significant. However, several randomized clinical trials suggested association of prolonged corticosteroids use with decreased inflammatory markers, duration of ventilation use, and length of ICU stay. These positive trends led to testing the effects of dexamethasone in treating ARDS patients.[35, 63-65]

With previous evidence, Jesus Villar and his coworkers conducted the first randomized clinical trial evaluating the efficacy of DEXs in ARDS 277 patients. The was a multicentered, single-blinded, randomized controlled trial with patients with acute onset or moderate to severe ARDS. The DEX group had higher ventilator-free days and lower mortality rate within 60 days than the control group. The incidence of adverse events between the two groups was also statistically insignificant. Common adverse events in ICU were hyperglycemia (76% DEX group vs 70% control group), new infections such as sepsis or pneumonia (24% vs 25%), and barometric trauma (10% vs 7%). While the results were supportive, there were several shortcomings and areas to further explore. The study could not be generalized by overall patient population. The exclusion of patients with corticosteroids use and severe Chronic Obstructive Pulmonary Disease (COPD) especially limited the possible benefit of DEX in corticosteroid users. As many chronic inflammatory and respiratory diseases involve some form of corticosteroid treatment, further investigation is necessary.[2]

There are several studies that support DEX's anti-inflammatory mechanism specific to respiratory airways (nasal cavity, bronchi, and alveoli). One study, compared different glucocorticoids (methylprednisolone, defazacort, budesonide, and dexamethasone) on eosinophil survival with cultures from nasal mucosa and polyps. The inhibitory potencies (**Table 4**) were compared across the four steroids by measuring their IC50. Among the four steroids, dexamethasone and budesonide were most efficient at preventing eosinophil survival in nasal mucosa (58nM). On nasal polyp, DEX had the highest inhibitory potency (76nM).[66] Another study also suggested roles of eosinophils modulating inflammatory response and activation in ARDS patients. ARDS patients displayed higher levels of eosinophils, thus DEX's high inhibitory potency is a potential benefit to treat ARDS.[67]

Table 4: Effect of glucocorticoids on preventing eosinophil survival[66]

	Nasal Mucosa		Nasal Polyp	
	IC_{50} (nM)	Potency	IC_{50} (nM)	Potency
Methylprednisolone	536	1	546	1
Defazacort	264	2.1	390	1.4
Budesonide	58	9.4	76	7.2
Dexamethasone	58	9.4	76	7.2

IC_{50}= steroid concertation that inhibits 50% of eosinophil-induced survival.

Other studies have focused specifically on COX-2 repression by DEX. Induction of COX-2 expression releases inflammatory mediators in response to IL-1B. Airway epithelial cells respond to these inflammatory mediators by releasing more pro-inflammatory cytokines. Newton and coworkers explored how DEX controls the downregulation of COX-2 transcription using airway epithelial cells. They investigated the effect of DEX repressing COX-2 transcription and subsequent levels of prostaglandin E2 (PGE2) by comparing IL-1B levels. Both COX activity and PGE2 release decreased with increasing concentration of DEX **(Fig. 7A**). DEX's IC50 value for the inhibition of both COX-2 activity and PGE2 release was between 1nM-1000nM, showing inhibitory efficacy in airway epithelial cells. This not only showed evidence of COX-2 transcription repression but also translational repression. Through transcriptional arrest half-life experiments, DEX showed delayed decrease in COX-2 mRNA synthesis (**Fig. 7B**). This result further confirmed DEX's anti-inflammatory affect in respiratory passage by both repressing transcriptional and post-transcriptional activities.[68]

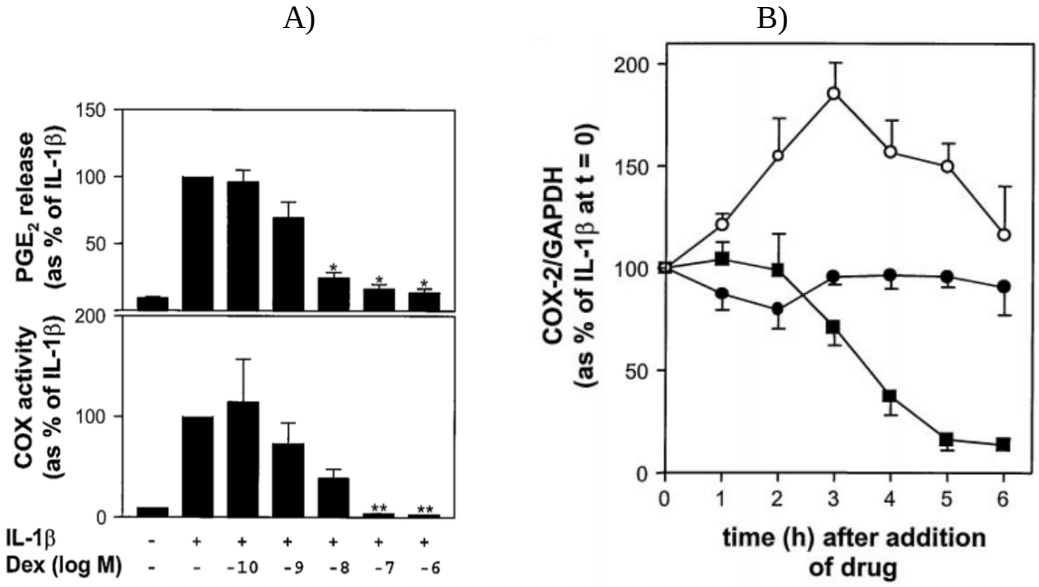


Fig. 7. DEX effects on COX-2 activity. **A)**DEX repression of COX-2 activity and PGE2 release measured in % of IL-1β **B)** ○, IL-1b; ●, IL-1b plus actinomycin D; ■, IL-1b plus dexamethasone. Actinomycin D prevents COX-2 repression activity of DEX. Transcriptional arrest half-life was measured and DEX delayed decrease in COX-2 mRNA synthesis[68]

Mitogen-Activated Protein Kinase (MAPK) p38 also affects COX-2 mRNA stability.[69] MAPKs are essential in immune cell proliferation, migration, and production of inflammatory cytokines. The MAPK signal is bistable, which can turn "on" or "off" mechanisms due to its own ability to propagate.[70] Once MAPK is phosphorylated by p38, it is activated by MAPK Kinase 6 (MKK6). This initiates the cascade of expressing proinflammatory genes, one of which stabilizes COX-2 mRNA. With knowledge of destabilizing untranslated region (UTR) in cytokines, an experiment was conducted to test DEX's affect in MAPK activity regarding COX-2 mRNA stability. The COX-2 transcript contains 22 copies of the same destabilizing UTR, AUUUA. The half-lives of COX-2 mRNA **(Table 5)** were compared among MKK6 control, MKK6 with DEX, and MKK6 with SB (p38 inhibitor). Both MKK6 with either DEX or SB showed similar trends of a decrease in mRNA half-life thus DEX can decrease COX-2 mediated cytokines in the airway by inhibiting the phosphorylation of MAPK p38. Affecting the stability of COX-2 mRNA, MAKP's influence on post-transcriptional activity plays an essential role in regulating the degree and duration of airway inflammation.[69,71]

Table 5: Half-lives of tetracycline-regulated β-globin Cox-2 reporter mRNAs in the presence of MKK6, dexamethasone, or SB203580[a].[69]

Transcript	Half-life[b] of transcript (hours)			
	Control	MKK6	MKK6+DEX	MKK6 + SB
β-globin-COX2.5	1.16	1.24	1.08	1.32
β-globin-COX1.4	1.24	2.06	1.29	1.07
β-globin-COX0.6	1.02	2.24	1.31	1.15
β-globin-COX0.1	1.26	4.16	1.65	1.64
β-globin-COX0.5	NM[c]	NM	NM	NM

[a] 1μM of SB20358 (P38 inhibitor) was added 30 min prior to the addition of tetracycline and 1μM dexamethasone was added 2 hours prior to the addition of tetracycline.
[b] Half-lives were calculated from plots of β-globin/GAPDH ratio against time.
[c] NM, not measurable

Annexin A1 in the respiratory pathway causes a decrease in inflammation through neutrophil detachment and transmigration.[57,72] Presentation of annexin A1 in the lungs has shown to down regulate neutrophil recruitment in acute lung injury triggered by intestinal ischemia-reperfusion.[73] Another study was conducted on lung transplant recipients with cystic fibrosis (CF). CF is often seen with bacterial infection that increases airway inflammation, primarily through neutrophils. The accumulation and necrosis of neutrophils can lead to bronchial obstructions. The transplant recipients with tracheobronchitis had evidence of necrotic neutrophils associated with degradation of annexin A1. The annexin A1 degradation to kDaA1-BP was observed in peripheral blood in CF patients thus, the signs of annexin A1 degradation can be a marker for neutrophil necrosis.[74]

Constitutively, annexin A1 was thought to be mostly induced in mature cells. However, one study suggested DEX induced the synthesis of annexin A1 in immature lymphoblastic cells. The cells without DEX treatment had more intracellular annexin A1. With DEX treatment, annexin A1 profoundly increased on outer membrane and decreased in intracellular portion. Within 12 hours, more annexin A1s were replenished intracellularly. These results align with DEX mechanism inducing the release and synthesis of annexin A1. The externalized annexin A1 prevents neutrophil attachment to endothelial cells resulting in less transmigration to the inflammatory sites.[75] Furthermore, a study suggested DEX's dependence on a calcium based mechanism to release annexin A1. Calcium fluxes are also caused by annexin A1 peptide Ac9-25, which is involved in L-selectin shedding of neutrophils. L-selectin is a cell adhesion molecule, which contributes to leukocyte rolling. DEX's mechanism of increasing the shedding of L-selectin further regulates leukocyte recruitment.[76-78]

Another example of DEX's epigenetic modification is the repression of histone acetyltransferase activity. IL-1B stimulates histone acetylation and granulocyte-macrophage colony-stimulating factor expression through p65 associated acetyltransferase. DEX represses the p65 activated histone acetyltransferase suggesting another mechanism by which it can decrease inflammation.[79] Another non-genomic action of DEX was found in airway epithelial Cl^- secretion. The Cl^- is driven by K^+ channels. DEX inhibits transepithelial Cl^-

channel by targeting different types of K^+ channels that are activated by Ca^{2+} and cAMP. The downregulation of these K^+ channels are through non-genomic activation without typical nuclear receptor activities.[80]

Another pathway that DEX regulates gene expressions are through AP-1 and NF-κB. One all-inclusive study by Al-Harabi and colleges, tested the effects of DEX on liposaccharide (LPS) induced acute lung injury, measuring inhibition of NF-κB, COX-2, and pro-inflammatory mediators (IL-6, TNF-α). IL-10 plays an anti-inflammatory role in limiting host immune response and causing damage to cells. While DEX increased the expression of IL-10, other cytokines that activate NF-κB and COX-2 decreased. Cytokines such as TNF-α and IL-6 are highly related to pathogenesis of acute lung injuries. DEX treated LPS group had significantly lower production of TNF-α and IL-6 (**Fig. 8)**.[81] DEX also decreases inflammation by downregulating AP-1 expressions on lung epithelial cells. AP-1 interacts with NF-κB and various other transcription factors involved in inflammatory gene expression. The expression of AP-1 factors (c-Jun and c-Fos) decreased with DEX treatment in human lung adenocarcinoma (pulmonary type-II epithelial cell). This result suggests AP-1's significant interaction with other transcription factors in DEX pathways.[82] Furthermore, AP-1 and NF-κB are not only involved in inflammatory pathways but also in cell proliferation, differentiation, and oncogenesis. This led to the exploration of DEX in controlling programmed cell death and treating certain types of cancers.[83,84]

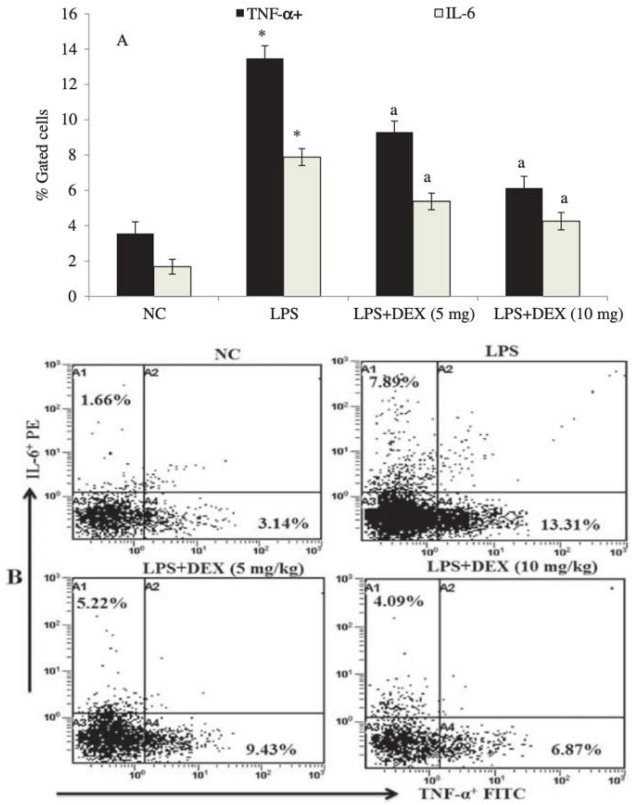


Fig. 8. Production of TNF-α and IL-6 in liposaccharide(LPS) treated cells. **A)** Flow cytometric analysis of DEX effect on total intracellular IL-6 and TNF- α. **B)** Each dot represents one mouse responsible for nocraml control (NC), LPS, LPS+DEX (5mg/kg), and LPS+DEX (10mg/kg) treated groups.[81]

3. DEX application in cancer regimen

3.1. DEX apoptosis pathways

Another group of pathways that DEX controls induces apoptosis (**Figure 9).** Specifically, one involves the activator protein 1 (AP-1) in cell proliferation and survival. AP-1, which is a transcription factor, dimerizes with two subunits, Fos and Jun. This dimer acts on the corresponding DNA responsible for transcription of cytokines and cell cycle regulators. DEX inhibits AP-1 and suppresses these transcriptions. As a result, repressed proliferation signals lead to cell death. Furthermore, AP-1 also regulates the tumor suppressor, p53. This also plays an important role in cell proliferation and survival.[83,84]

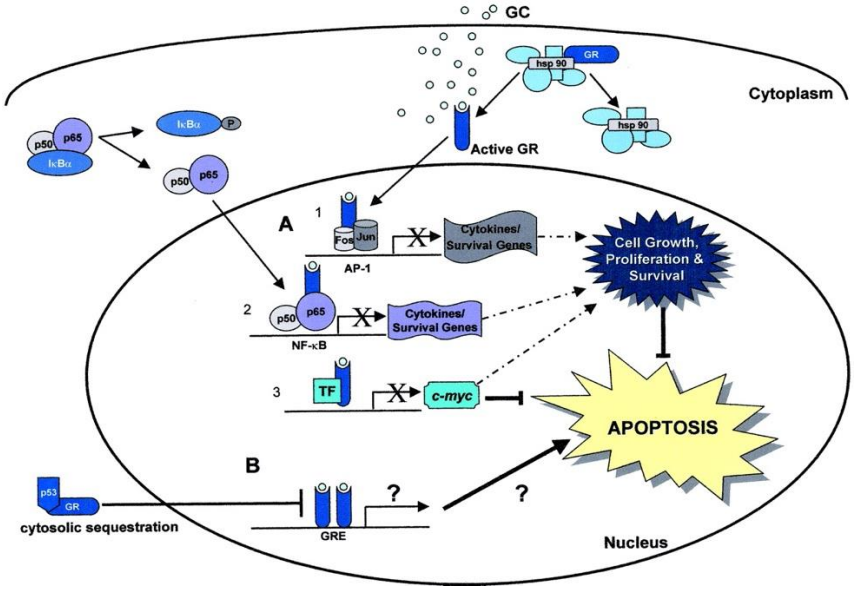


Fig. 9. DEX inducing apoptosis through controlling cell growth, proliferation and survival. A) DEX repressing AP-1, NF-κB, and c-myc proto-oncogene related gene activation B) Unknow upregulation of gene expression by DEX[84]

DEX also represses NF-κB, which ultimately leads to apoptosis. NF-κB is a heterodimer inhibited by NF-κB inhibitor alpha (IκBα). Once phosphorylated, NF-κB is released from IκBα. DEX can inhibit NF-κB by upregulating IκBα. synthesis. DEX also transrepresses survival gene expression by directly interacting with NF-κB. DEX competes with coactivators of preventing NF-κB DNA binding. Ultimately, a decrease in cytokines and survival factors halts cell cycle resulting in apoptosis.[84]

Lastly, DEX is involved in repressing c-myc proto-oncogene. Proto-oncogene expression has been demonstrated to inhibit apoptosis. Although the exact mechanism is unknown, DEX appears to interfere with the process of apoptosis. It is also unknown if DEX could upregulate the expressions of pro-apoptotic proteins to induce apoptosis.[84-87] DEX affecting the cell proliferation and survival pathways are key mechanisms in treating cancer such as lymphoma, leukemia, and multiple myeloma**.** Previously there has been attempts to use DEX as a monotherapy but most evidence supports synergy of DEX with other chemotherapeutic agents.[88-96] Thus, DEX is co-medicated to enhance chemotherapies and added adjunct to treat pains, loss of appetite, and chemotherapy induced nausea and vomiting (CINV).

3.2. Acute lymphoblastic leukemia (ALL) and multiple myeloma (MM)

Acute lymphoblastic leukemia (ALL) is most prevalent in pediatric population but it affects all ages.[97] ALL develops due to malignant transformation of lymphoid progenitor cells, which ultimately develops into B cells, T cells, and Natural Killer (NK) cells (**Fig. 10**). These immune cells play key roles in fighting infections. The malignant transformation occurs due to genetic mutation that prevents cell differentiation, inducing abnormal cell proliferation. ALL is largely divided into two groups, B-cell and T-cell ALL. While B-cell ALL has multiple subtypes based on genetic variations, T-cell ALL has insufficient evidence for unique subgroups.[98-101]

Conversely, multiple myeloma (MM) is specifically due to malignancy in plasma B-cells. This also affects the bone matrix, due to increased osteoclastic activity and decreased osteoblastic activity. The pathogenesis of MM correlated to monoclonal gammopathy of undetermined significance (MGUS). MGUS present with abnormal monoclonal protein and high risk of fractures. The abnormal monoclonal proteins are made from bone marrow and is highly associated with developing MM. Another key pathogenesis involves bone marrow microenvironment (BMM). BMM is responsible for malignant transformation and disease progression. BMM provides condition for repair and response to various signals allowing cells to proliferate, transmigrate, and attach. BMM also produces inflammatory modulators such as IL-6, TNF-α, VEGF, adiponectin, and leptin in bone marrow promoting malignancy.[102]

While ALL in children have 98% complete remission rate with a 90% cure rate, 80-90% of adults reach complete remission and only 40% of them are cured. Compared to ALL, MM is only treatable and the complete remission occurs for 30-40% of patients after transplantation.[103-105] For this, achieving remission in both MM and ALL is important. DEX has shown to induce remission for both ALL and MM via its cytotoxic effect and by decreasing leukocytes traveling to areas of cancerous cells causing inflammatory damage and pain.[106-108]

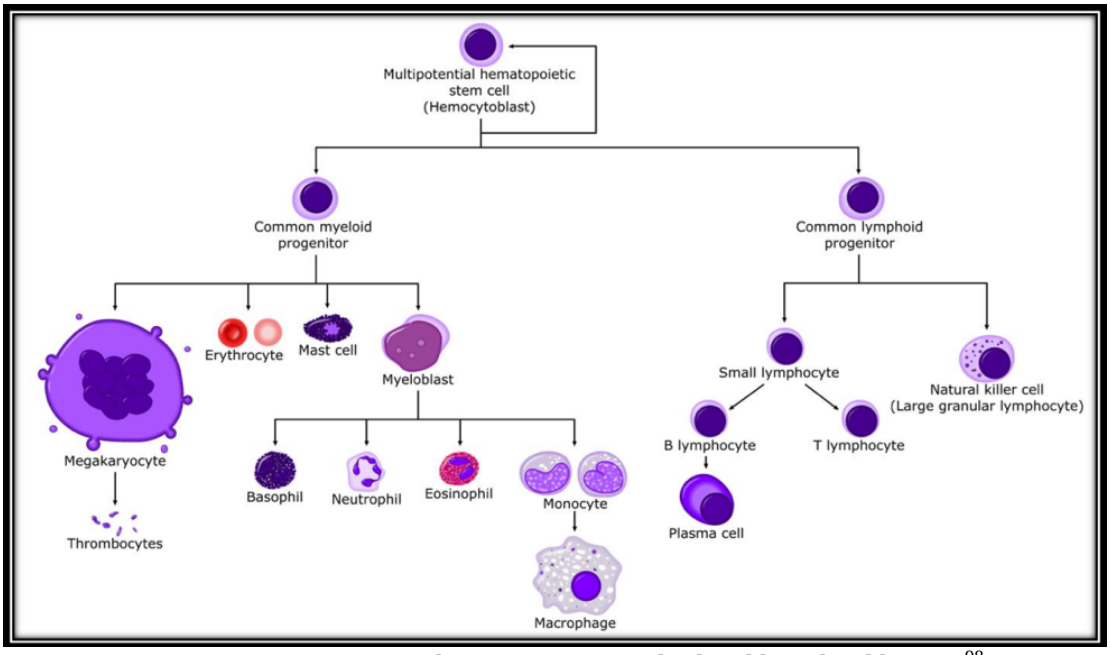


Fig. 10. Hematopoiesis in bone marrow: myeloid and lymphoid lineage[98]

3.2.1. DEX use in treating ALL

The standard of practice to treat ALL include combination of vincristine, L-asparaginase, a corticosteroid, and with or without anthracyclines. Previously, prednisolone was used in the combination to treat ALL. This practice changed as more studies supported DEX's association with improved event-free survival and higher cytotoxicity than prednisolone.[106,109-112] One of the comparative studies was conducted by Kasper and coworkers, comparing antileukemic activity of DEX and prednisolone. DEX had higher cytotoxicity than prednisolone when comparing their LC_{50} on ALL cells. DEX had LC_{50} of 0.2 μM while prednisone had much lower potency with LC_{50} of 3.5 μM.[106] Several randomized clinical trials also suggested DEX's association with lower 5-year cumulative incidence relapse and higher 5-year event free survival rate. However, DEX was also associated with higher incidence of infections, osteonecrosis, and induction-related death rate. Although there was no difference in overall survival rate, positive results in relapse and event-free survival rate are key benefits of DEX.[110,113] Ultimately, having higher cytotoxicity can lead to fewer relapses and improve survival but also increase incidence of adverse events. As a result, treatment balance is necessary for ALL patients to maximize beneficial effects of DEX and minimize side effects.

3.2.2. MM treatment with DEX

DEX in combination with proteasome inhibitor and immunomodulatory agent can treat MM.[107,108,114,115] DEX is also used before starting chemotherapeutic agents to prevent hypersensitivity reactions. The combination therapy with DEX enhances cytotoxicity with its cell-cycle arrest and apoptotic mechanism. For instance, adding DEX to lenalidomide to relapsed MM patients improved response rates up by 30%.[116] DEX is not only used in initial management but also in relapsed or refractory MM (RRMM).[117] One RRMM treatment includes the combination of Daratumumab and pomalidomide with DEX. DEX with pomalidomide had greater progression-free survival (PFS).[118] Furthermore, even after failing with attempts for three or more agents (lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab), DEX with Selinexor demonstrated efficacy in treating RRMM.[119-121]

For transplant eligible patients, DEX is primarily added to the initial combination therapy. Prednisone is another corticosteroid used with melphalan in MM treatment combination. While prednisone-melphalan based treatment is the primary choice for transplant ineligible patients, this treatment regimen should be avoided in transplant eligible candidates. Melphalan, an alkylating agent, is avoided in transplant candidates to spare normal hematopoietic precursors. Thus, DEX-based regimen is preferred over prednisone-melphalan for transplant eligible patients.[108,122,123] Another study compared DEX and prednisone when treated with melphalan on elderly patients with MM. Although there was no significant difference in event free survival (EFS) rate, DEX based regimen had higher complete response rate after 12 cycles.[124]

4. Fluid retention and weight gain side effects

GCs have similar structures to aldosterone, which is a mineralocorticoid (MC) and responsible for controlling blood pressure by decreasing sodium excretion. DEX is known to have very low MC activity. A study revealed much higher binding affinity of DEX to GC receptor (9.8nM) compared to MC receptors (23.9nM). Conversely, aldosterone has much higher

affinity to MC receptor (0.86nM) than GC receptor (92nM).[125] GCs and aldosterone can both bind to MC receptors but GCs are less efficient in stimulating MC receptors. MC receptors specificity requires 11beta-hydroxysteroid dehydrogenase type 1 (11-β-HSD1) to catabolize cortisone into cortisol (active metabolite). While this catabolic action happens in most tissues, 11beta-hydroxysteroid dehydrogenase type 2 (11-β-HSD2) inactivates cortisol to cortisone in the kidney **(Fig. 1)**. However, high dose or a long-term use of potent glucocorticoid such as DEX is possible to stimulate the MC receptor specifically in the kidneys retaining sodium and water.[126-131]

Moreover, the weight gain mostly comes from excess level of GCs promoting gluconeogenesis in the liver and decreasing glucose uptake and utilization. One of the severe side effects of DEX is Cushing's syndrome. Patients on long-term or high dose DEX treatment present with central obesity characterized with muscle weakness, moon face, weight gain, and fat-redistribution (buffalo hump).[132,133] Also, increase in appetite further contributes to the weight gain by inhibiting leptin (satiety hormone) synthesis and secretion.[134]

5. COVID-19: ARDS, cytokine Storm, and cutaneous manifestation

The novel coronavirus disease 2019 (COVID-19) has already affected more than 16,000,000 people and caused over 600,000 deaths.[135] The more specific term for COVID-19 is sever acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 is highly contagious in person-to-person transmission.[136] Coronaviruses (CoV) are family of positive-strand RNA viruses divided into α, β, γ, and δ classifications. Among these classes, β-CoV is highly pathogenetic which is the class that causes COVID-19.[137] Patients can be asymptomatic and the severity of disease varies from mild to severe symptoms (fever, cough, myalgia, diarrhea, dyspnea, respiratory distress, sepsis, and septic shock). Although there are more mild and asymptomatic patients, a considerable number of patients need intensive care due to severe acute respiratory syndrome (SARS) progressing to respiratory failure. To treat these critically ill patients, DEX has been tested to modulate inflammatory lung injuries, which can potentially prevent respiratory failure and death.[138-141] From the RECOVERY trial, DEX was assigned to 2104 patients and other 4321 patients received usual standard of care. The DEX group (21.6%) had a lower death rate than the usual care group (24.6%). Furthermore, the DEX group had reduced death by one-third among patients receiving oxygen without invasive mechanical ventilation but no change compared to those without initial respiratory support.[1] This suggests the importance of mechanical ventilation support and benefit of DEX in treating patients. There are also several other case reports supporting the benefits in using DEX for severely ill COVID-19 patients.[142-164]

Another severe presentation of COVID-19 is associated with hypercytokinemia, also known as the cytokine storm. Although many patients had milder conditions, more severe cases can lead to sudden deterioration in the process of recovery. The coronavirus itself causes damage, but a large portion of damage also comes from patient's own immune response. High levels of cytokines are correlated to more severe COVID-19 patients and the cytokine storm is one of the main cause of ARDS and multi-organ failure.[145] In addition to respiratory failure, extra-pulmonary organ failures are associated with cytokine storms. This is even more prominent when non-pulmonary organ failure occurred without respiratory failure in COVID-19 patients.[146] Higher mortality rates are associated with the

degree of increase in serum cytokine levels.[147] Moreover, higher expressions of IL-1B, TNF-α, IL-6, and IL-2R, which are inflammatory cytokines, are observed in COVID-19 patients. Although early administration of DEX can depress patient's immune system to clear the virus, it can help critically ill patients with high probability of inflammatory cytokine induced ARDS. Conversely, higher levels of IL-4 and IL-10, which are anti-inflammatory cytokines, were also seen in COVID-19 patients. Along with immunosuppression, DEX could also decrease anti-inflammatory cytokines. This has led to a divided consensus in using DEX.[148-149]

In addition, several case reports suggest cutaneous manifestation associated with COVID-19. Without respiratory distress and a history of taking drugs, a patient presented with a generalized rash with low-grade fever. The lesions were petechial and maculopapular, distributed on face, neck, abdomen, buttocks, and extremities.[150] Another form of cutaneous manifestation was specifically on the toes also called as "covid toe" or pseudo-chilblain. The patient had painful plaques and redness on his toe. Similar characteristics of cutaneous manifestation was also found in several other patients on their toes and fingers.[151-153] Based on analyzing 375 cases, classification of COVID-19 associated cutaneous manifestation was made. Among the cases, maculopapular eruptions (47%) was most common and erythema with vesicles (19%) and urticarial lesions (19%) followed. Over half of the pseudo-chilblain cases appeared after presenting other symptoms of COVID-19.[154] While some cutaneious manifestations were localized, many of them were dispersed suggesting potential systemic DEX use.

7. Conclusion

Understanding DEX's multiple mechanisms and pathogenesis for diseases can improve recommendations in treating patients. Because DEX is an anti-inflammatory agent and an immunosuppressant, duality in treatment consideration exist. While anti-inflammatory function can help symptomatic alleviation and decrease cytokine levels, immunosuppressive quality can delay elimination of the pathogens and recovery. There are patients who are already on chronic GC while some are treatment naive. Due to its various applications, it is important to assess appropriateness and correct dosing schedule for each patient to prevent adverse events.

Although pathogen themselves can damage cells, a large portion of damage comes from patient's own immune response causing inflammation. Severe inflammation presents with pain, fever, organ damage, and decrease in quality of life. Moreover, immune system overdrive can cause cytokine storm which has a high morbidity and mortality rate. The degree of elevated cytokine levels are associated with patients with ARDS and severity of organ damage. This suggest the potential benefit of DEX and significance of controlling cytokine levels to prevent further damage and worsening outcomes.

Although there is no proven specific treatment for COVID-19 and ARDS, there is ongoing progress in managing the patients. More areas should be explored in finding incidence of COVID-19 in long-term GC treated patients and efficacy of DEX in this population. Based on previous knowledge of ARDS, mechanism of DEX, and upcoming studies on the benefit of DEX in COVID-19 outcomes, more firm and preventative recommendation may be established in near future.

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