BioGecko Vol 12 Issue 02 2023

ISSN NO: 2230-5807

GLUCOCORTICOID ANTIINFLAMMATORY ACTION: NOVEL PATHWAYS FOR EXISTING MEDICATIONS

Dr.Debipreeta Dutta,
Assistant Professor, Department of Zoology, Gurucharan College, Silchar, Assam
Email: dr.debipreetadutta@gmail.com

Abstract:
In certain individuals with asthma, rheumatoid arthritis, and inflammatory bowel disease, glucocorticoid resistance or insensitivity is a significant obstacle to therapy. Increased P-glycoprotein-mediated drug efflux, increased macrophage migration inhibitory factor, and activation of mitogen-activated protein (MAP) kinase pathways by specific cytokines are all examples of identified molecular mechanisms of glucocorticoid resistance. Broad-spectrum antiinflammatory drugs like calcineurin inhibitors and other immunomodulators, as well as novel antiinflammatory drugs like phosphodiesterase 4 or nuclear factor B inhibitors, can be used to treat patients who have developed resistance to glucocorticoids, but all of these drugs are associated with significant risks. In order to treat glucocorticoid resistance, it may be possible to reverse the condition by interfering with its underlying processes. Theophylline, antioxidants, and phosphoinositide-3 kinase- inhibitors are all examples of drugs that may be used to activate HDAC2 expression, as are the inhibitors of macrophage migration inhibitory factor and P-glycoprotein. Haemoglobin (Hb) may be both poisonous and proinflammatory, yet specialised mechanisms can filter it out of the bloodstream and from injury sites with remarkable efficiency. Major Hb-clearing cells are macrophages, and CD163 was shown to be the particular haemoglobin-haptoglobin scavenger receptor only very recently (HSR). We demonstrate that dexamethasone significantly increased CD163 mRNA transcription (13-fold) and cell surface expression (10-fold) by human macrophages, allowing for the selective absorption of haemoglobin-haptoglobin complexes. Interleukin 4 (IL-4) is a TH2 cytokine that totally downregulated CD163 expression. After 4 hours of macrophage-ligand interaction, the functional receptor modulation range reached a factor of 100. These findings support that glucocorticoids' enhancement of Hb clearance represents anantiinflammatory effect.

Keywords: Glucocorticoids, haptoglobin, haemolysis.

Introduction:

For many inflammatory and immunological illnesses such asthma, rheumatoid arthritis, inflammatory bowel disease, and autoimmune diseases, glucocorticosteroids (glucocorticoids; often known as corticosteroids or steroids) are the most effective antiinflammatory therapy available. However, some people with these disorders respond poorly or not at all to large doses of glucocorticoids. Glucocorticoid resistance seems to be common in several inflammatory disorders, including chronic obstructive pulmonary disease (COPD), interstitial lung fibrosis, acute respiratory distress syndrome, and cystic fibrosis. Since chronic inflammatory disorders are so common and, on the rise, glucocorticoid resistance or insensitivity is a major hurdle to successful treatment that contributes significantly to chronic inflammation's high cost. We explore glucocorticoid resistance and the recently identified molecular underpinnings of glucocorticoid resistance that may be susceptible to novel treatment methods for treating inflammation that has become resistant to corticosteroids.

Most investigations of glucocorticoid resistance have been conducted on asthma, however there is growing evidence that glucocorticoid resistance is also present in a wide variety of other allergy and chronic inflammatory illnesses. The definition of glucocorticoid resistance varies widely and its prevalence is difficult to gauge because of these factors.

Haemoglobin (Hb) is released in enormous quantities from rupturing erythrocytes, and this process is linked to several clinical diseases include haemolysis and bleeding. The haem moiety of cell-free Hb catalyses the generation of reactive oxygen species (ROS) during oxidation and subsequent dissociation from methemoglobin, leading to oxidative stress, stimulation of inflammatory responses, and tissue damage (Lim et al., 1998; Wagener et al., 2001). Consequently, it seems that the quick removal of free Hb is a key function, and highly effective scavenging mechanisms have developed to minimise the harmful effects of Hb. Macrophages in the liver, spleen, and bone marrow remove free Hb by binding it strongly to the acute-phase blood protein haptoglobin (Hp). Up until recently, it was thought that the macrophage-restricted CD163 antigen was the particular haemoglobin scavenger receptor (HSR), but the molecular processes involved in the elimination of Hb-Hp complexes remained unknown (Kristiansen et al, 2001). CD163 is a surface protein on cells that is part of the scavenger receptor cysteSchmelzbergstrasse 51, CH-8044 Zurich, Switzerland. Dr. Dominik J. Schaer. For correspondence, please write to schaerdominik@ hotmail.com. domain-containing (DDB) protein family (Law et al, 1993; Schaer et al, 2001). The fact that it binds and internalises Hb-Hp complexes but not free Hb or free Hp suggests that the Hb-Hp complex exposes a neo-epitope (Kristiansen et al, 2001). Accumulation of CD163-expressing macrophages has been seen during the resolution of acute inflammatory responses, in chronic inflammatory illnesses like psoriasis, and in the healing of wounds (Zwadlo et al, 1987; Djemadji-Oudjiel et al., 1996). Moreover, the fact that the glucocorticoid dexamethasone has been shown to induce the CD163 antigen suggests the HSR may have a role as an antiinflammatory protein (Hogger et al, 1998; Schaer et al, 2001). In this study, we provide a hitherto unreported activity of dexamethasone—the robust promotion of Hb uptake by macrophages—and suggest a new antiinflammatory route involving the HSR. For further details readers can check the articles (Gaballa, et al. 2021, Kourakis, et al. 2021,
Russell, et. al. 2020, Bruscoli, et al. 2021)

Glucocorticoid-resistant asthma:

Inhaled corticosteroids have replaced long-term use of oral medications for the majority of people with asthma because of their efficacy in controlling symptoms at lower dosages.
1 Only around 10% of patients, on average, need the highest possible inhaled dosage, and only about 1% require frequent therapy with oral glucocorticoids (termed glucocorticoid-dependent asthma). No clinical improvement following therapy with high-dose oral glucocorticoid (prednisolone 40 mg daily for 2 weeks) identifies a small subset of individuals as glucocorticoid-resistant. 2 Although a single injection of a depot glucocorticoid (triamcinolone acetonide) or a trial of oral glucocorticoids may be utilised to identify people who are totally resistant, there are no well established procedures for the assessment of clinical glucocorticoid responsiveness.
In 1968, the first cases of asthmatic glucocorticoid resistance were reported; these six patients showed no clinical improvement after receiving large doses of systemic glucocorticoids.
It was observed by Carmichael and coworkers4 that in a larger sample of 58 patients with persistent asthma, oral prednisolone (20 mg daily for at least 7 days) did not improve lung function (i.e., forced expiratory volume in 1 s climbed by less than 15%). Compared to glucocorticoid-sensitive individuals, those with glucocorticoid-resistant asthma had more severe symptoms for a longer period of time, had reduced morning lung function, exhibited higher levels of airway hyperresponsiveness, and had a more common family history of asthma.
Patients' descriptions of cortisol deficiencies and sex hormone abnormalities do not apply to these individuals. that runs in the family; genetically predisposed to be resistant to corticosteroids. Patients with glucocorticoid-resistant asthma, who often experience the Cushingoid side effects of corticosteroids, have normal plasma cortisol and adrenal suppression in response to exogenous glucocorticoids.
This shows that there is a deficiency in the antiinflammatory effects of glucocorticoids, as opposed to a flaw in their metabolic or endocrine effects, since the lack of response to oral glucocorticoids cannot be explained by lower gastrointestinal absorption or other pharmacokinetic processes. Patients with

glucocorticoid-resistant asthma reported greater eosinophil and lymphocyte counts in their bronchial biopsy samples after receiving high doses of glucocorticoids than patients with glucocorticoid-sensitive asthma. Furthermore, the T-helper-2 (Th2) cytokines interleukin and interleukin were not suppressed in cells from individuals with resistance to glucocorticoids in bronchoalveolar lavage. It has been found that bronchoalveolar lavage fluid from patients with glucocorticoid-resistant asthma has a higher ratio of matrix metalloproteinase (MMP) to tissue inhibitor of MMP (TIMP) 1 than lavage fluid from patients with glucocorticoid-sensitive asthma, and that macrophages from patients with resistance do not show the normal rise in TIMP1 after corticosteroid treatment in vitro. Patients with glucocorticoid-resistant asthma may have aberrant tissue remodelling in the airways due to a deficiency in TIMP1 synthesis; this abnormal remodelling may contribute to the diminished bronchodilator (reversibility) response in these patients.

Insensitivity to corticosteroids has been linked to asthma severity, as people with severe asthma are less sensitive to glucocorticoids than those with moderate asthma. The amount of glucocorticoids required to alleviate symptoms is, in fact, a good indicator of the severity of asthma. On the other hand, glucocorticoid insensitivity might also affect certain people with milder forms of asthma. Tobacco use is associated with a worsening of asthma symptoms, a faster deterioration in lung function, and a lower response to inhaled and oral glucocorticoids in around 25% of asthmatic patients.

Patients with glucocorticoid-resistant asthma have circulating cells that respond poorly to glucocorticoids in vitro, a crucial discovery that has inspired a number of following molecular research. Monocyte and peripheral blood mononuclear cell (PBMC) complement receptor proliferation induced in vitro by phytohaemagluttinin was totally inhibited by steroids in individuals with glucocorticoid-sensitive asthma. Patients with glucocorticoid-resistant asthma had circulating Tlymphocytes and monocytes, but they showed no signs of suppression of proliferation in response to steroid therapy. Subsequent research revealed that in individuals with glucocorticoid-resistant asthma, glucocorticoids did not suppress monocyte activity or interleukin-2 and interferon- production in PBMCs in response to phytohaemagluttinin stimulation. Compared to individuals with glucocorticoid-sensitive asthma, those with severe asthma that was not controlled with high doses of inhaled corticosteroids had a reduced inhibitory impact of glucocorticoids on secretion of cytokines and chemokines from peripheral monocytes and alveolar macrophages. The skin blanching reaction to topical glucocorticoids was similarly diminished in patients with glucocorticoid-resistant asthma compared to glucocorticoid-sensitive persons, indicating a systemic imbalance in glucocorticoid responsiveness.

Other chronic inflammatory and immunological disorders that often respond:

The majority of patients with severe illness respond poorly to glucocorticoids, although people with the moderate or early disease might also have a poor clinical response. Patients with glucocorticoid-resistant rheumatoid arthritis have peripheral blood mononuclear cells (PBMCs) that have a reduced antiproliferative and cytokine response to corticosteroids in vitro19,20 compared to cells from patients with the glucocorticoid-sensitive disease, similar to what is seen in glucocorticoid-resistant asthma. Not only do some people with Crohn's disease and ulcerative colitis not respond to steroids clinically, but their circulating lymphocytes also respond less strongly to glucocorticoids than they do in glucocorticoid-sensitive people. Some people with SLE have a poor clinical response to glucocorticoids and a lower T-cell response in vitro.

Topical glucocorticoids have failed to help certain individuals with atopic dermatitis.

COPD:

High dosages of inhaled or oral glucocorticoids are usually ineffective for individuals with COPD, in stark contrast to patients with asthma. The effectiveness of glucocorticoids in slowing disease progression or increasing survival has been called into doubt more recently, however they have been shown to reduce exacerbations by a minor amount. Inflammation in the sputum and airways of COPD

patients and cytokine responses in alveolar macrophages in vitro have been found to be unaffected by inhaled corticosteroids. Asthma is likely present in the 10% of COPD patients who exhibit a clinical response to inhaled corticosteroids; larger levels of eosinophils characterise these individuals in the airways and greater reversibility to bronchodilators.
Inflammatory disorders that often do not respond to glucocorticoids
Patients with cystic fibrosis suffer from chronic airway inflammation and frequent infective flare-ups, yet inhaled corticosteroids have not been shown to improve clinical outcomes and may even stunt development in children with CF.
Also, while there have been few large controlled trials, clinical investigations have demonstrated that oral glucocorticoids are ineffective for treating interstitial pulmonary fibrosis (also known as typical interstitial pneumonia), which is characterised by persistent inflammation of the lung parenchyma. Acute respiratory distress syndrome patients, who have a severe inflammatory reaction in their lungs, also do not respond well to large doses of systemic glucocorticoids.
Furthermore, inflammation plays a crucial role in the progression of atherosclerosis, yet glucocorticoids have little therapeutic advantage in the management of cardiovascular disease or the prevention of the formation of atheromatous plaques.

Side-effects:
Patients who are glucocorticoid-resistant may still have negative consequences, despite the fact that the drugs' antiinflammatory effects are reduced or non-existent. Because of the large dosages of glucocorticoids often prescribed to these patients, they may be at a higher risk of experiencing negative side effects. Unlike the main methods utilised by corticosteroids to control inflammation, the molecular processes behind the systemic adverse effects of glucocorticoids are not well known. Important insights into the molecular processes of glucocorticoids may be gleaned from the observation that glucocorticoid resistance arises in tandem with glucocorticoid adverse effects.

Defeating inflammation by use of glucocorticoids:
Research into the proinflammatory and antiinflammatory genes that glucocorticoids activate and repress has led to significant breakthroughs in our knowledge of the molecular processes by which glucocorticoids control inflammation.

Gene activation:
Glucocorticoids attach to glucocorticoid receptors in the cytoplasm, which allows them to exert their effects on the cell from the outside.
Activated glucocorticoid receptors quickly translocate to the nucleus upon ligand binding, where the receptor complex exerts its molecular effects after being liberated from chaperone proteins (such as heat shock protein 90 [HSP90]). The nuclear import proteins importin (karyopherin) and importin are essential for the nuclear translocation process.
Only the alpha subtype of the glucocorticoid receptor (GCR) binds to glucocorticoids. An alternatively spliced type of glucocorticoid receptor, glucocorticoid receptor, binds to DNA and may function as a dominant-negative inhibitor of glucocorticoid action by preventing the binding of activated glucocorticoid receptor to DNA.
To activate (or in some cases repress) transcription of glucocorticoid-responsive genes, glucocorticoid receptors homodimerise and bind to glucocorticoid response elements (GREs) in the promoter region of these genes. Interaction between the DNA-bound glucocorticoid receptor and transcriptional coactivator molecules (like cyclic AMP response element binding protein) that have intrinsic histone acetyltransferase activity and cause acetylation of core histones (particularly histone 4) can also activate glucocorticoid-responsive genes. After RNA polymerase II interacts with acetylated histones, gene activation occurs. This is because acetylated histones function as a magnet for chromatin remodelling engines like SWI/SNF proteins. Genes encoding 2-adrenergic receptors, the antiinflammatory proteins secretory leucoprotease inhibitor and mitogen-activated protein kinase

phosphatase 1 (MKP1), which inhibits MAP-kinase pathways, are all turned on by glucocorticoids. 46,47 The suppression of osteocalcin, a protein involved in bone formation, is thought to be partly mediated by the glucocorticoid receptor's interaction with negative GREs or GREs crossing the transcriptional start site.

The Clinical Relevance of Genomic and Non-Genomic Mechanisms of Action:

Glucocorticoids have a role in a wide variety of regulatory processes, including energy and lipid metabolism and stress adaption. At doses above the physiological glucocorticoid levels, two of its most significant actions, antiinflammatory and immunosuppressive, become apparent.

It depicts the genetic and non-genomic methods of action of glucocorticoids and synthesized glucocorticoids, respectively (7). It is only after GC, in its lipophilic form, crosses cell membranes and binds to the multiprotein complex of chaperones (e.g., Hsp40, Hsp56, Hsp70, and Hsp90), immunophilins that act as co-chaperones (e.g., p23, FKBP51, FKBP52), and the intracellular cytoplasmic glucocorticoid receptor, that genomic mechanisms (cGR). Translocating to the nucleus and binding to glucocorticoid response regions in DNA occurs after the GC-cGR complex binds to and dissociates from these proteins. The end result is transrepression, in which the transcription of genes encoding inflammatory cytokines (like interleukin-6 and interleukin-8 and tumour necrosis factor-a) is suppressed, and transactivation, in which the transcription of antiinflammatory genes (like interleukin-10 and IB and annexin A1) is stimulated.

It takes around 30 minutes after GC injection for the genomic pathways to become obvious. On the other hand, the effects of a second class of non-genetic pathways may be seen within minutes after dosing. Changes in cellular membranes, inhibition of the phospholipase A2 enzyme, and contact with membrane glucocorticoid receptors facilitate these non-genomic effects (mGR). Kinases, such as p38 MAP kinase, are examples of second messengers. The end result is a reduction in lymphocyte activity and proliferation.

Due to differences in the detrimental effect profile and activation caused by different glucocorticoid doses and preparations, identifying genomic and non-genomic pathways is therapeutically relevant. Low (7.5 mg prednisone equivalent per day) to moderate (7.5-30 mg prednisone equivalent per day) GC dosages activate genomic effects, whereas high-doses over 30 to 50 mg per day gradually saturate cGRs. According to this pharmacological theory, dosages of prednisone beyond 50 mg daily approach the maximum of cGR saturation, providing no further antiinflammatory benefit while raising the potential for side effects. Certain side effects, including avascular bone necrosis, depend on the maximum GC dosage and the length of time at a high dose (the rate of tapering).

High GC doses, such as those achieved with methylprednisolone pulses, trigger non-genomic processes. This activation begins at 100 mg of prednisone and peaks at 250 mg to 500 mg. The shorter time of administration is suggested to be one reason why effects mediated by non-genomic pathways are linked with less side effects than those mediated by genomic systems [11]. Different GC preparations have varying degrees of activation of these genomic and non-genomic pathways. Dexamethasone and methylprednisolone, for instance, activate the non-genomic pathway at a rate three times higher than prednisone. The length of hypothalamic-pituitary-adrenal axis suppression and the mineralocorticoid effects of different GC preparations also vary. This review does not include other aspects that contribute to the degree of GC-axis suppression and, by extension, the severity of side effects, such as time of administration (less suppression when delivered in the morning) and their chronopharmacology.

Identifying solutions to reduce GC toxicity requires an understanding of these processes. Figure 2 depicts the delivery of GCs in current clinical studies, which often begins with intravenous methylprednisolone pulses (to activate non-genomic pathways) and is then followed by lower peak oral GC doses and quicker tapering of oral GCs. This approach seeks to reduce the risk of GC-related side effects without sacrificing therapeutic efficacy.

Adverse events in connection with glucocorticoids:

Evidence links organ damage in SLE to disease activity and glucocorticoid exposure (15, 16). Several of the described trials are flawed due to confounding by indication, since greater GC dosages are often supplied to patients with higher disease activity (i.e., patients with more severe activity are administered higher GC doses). It is often difficult to separate organ damage produced by prednisone from that caused by disease activity or concurrent immunosuppressive medicines since damage is often assessed by indices that aggregate various symptoms [for example, the SLICC/ACR damage index (SDI)] [17]. Third, there is the issue of temporal bias in many studies because the damage caused by disease activity is often larger in early stages, whereas the damage caused by GC becomes steadily worse as the illness progresses.

By 5 years of diagnosis, 50% of people with SLE will have organ damage, and the risk increases by 2.8% for every 1 mg of prednisone used daily. It has been observed that reducing the maintenance dosage of prednisone to below 6.0 to 7.5 mg per day and attaining illness remission [15, 20] may help reduce the risk of organ damage [21–23].

Adverse effects from GC have been broken down into two groups: those caused by large dosages administered rapidly, and those caused by cumulative GC doses. Using intravenous methylprednisolone pulses, the peak oral-GC dosage, the length of exposure to high-GC doses, and the GC cumulative dose, Table 1 summarises the documented GC side effects.

Medicine and biology as maintenance:

While data are currently few, there is mounting indication that using some biologics during the maintenance phase may help in establishing durable remission. Patients on glucocorticoids may benefit from the RITUXIRESCUE regimen, which consists of rituximab plus methylprednisolone without an increase in oral GC dosage. There was a 78% response rate in LN relapses with this regimen, and more than 50% of patients were able to reduce or stop oral GC as a result of it during follow-up.

No flares occurred during follow-up without the requirement for maintenance treatment above 5 mg of prednisone daily after an Italian approach of four 375 g/m2 rituximab doses reinforced by two extra doses at 1 and 2 months later (4+2 rituximab scheme). The possibility of rituximab as a maintenance medication enabling glucocorticoid discontinuation has been recognised in other, smaller investigations. Because rituximab has not been clinically evaluated for maintenance, its administration may help in reducing flares during GC withdrawal, but more research is needed.

After the induction phase, patients in the BLISS-LN study who received belimumab in addition to standard of care medication (either MMF or cyclophosphamide with GC) maintained a constant glomerular filtration rate for up to 2 years. In addition, preliminary reports have shown that belimumab treatment may permit decrease or discontinuation of maintenance GCs; nevertheless, this needs additional research.

Moreover, the NOBILITY study found that patients who received obinutuzumab in addition to standard of care medication had a greater chance of achieving a durable response, a higher glomerular filtration rate, and an improved serological profile at 76 weeks and beyond. The results of this study show that B cell targeted treatment may pave the way for GC removal or, at the very least, a safe decrease to 5 mg/d of prednisone.

Conclusions:

Recent medication advancements in lupus nephritis encourage the use of lower glucocorticoid dosages, however it is important to remember that "one size does not fit all" patients. Patients presenting with severe lupus nephritis with a glomerular filtration rate of 30 mL/min/1.73 m2 or less have been excluded from most clinical studies, and there is no evidence to support the efficacy of decreased glucocorticoid dosages in this group of patients. Several of the studies that have been published are also observational reports from a single institution, which makes them vulnerable to

bias. That's why it's important to proceed with care when deciding on a glucocorticoid treatment plan, and to assess each individual patient on an individual basis.
Research into lupus nephritis's future will likely focus on finding the safest and most effective way to treat the disease without the use of glucocorticoids. Combination studies combining calcineurin inhibitors, biologic medicines, or complement inhibitors with current treatment protocols might help achieve this goal.
Its negative side effects have always outweighed GC's antiinflammatory effects. Peak dosages, exposure periods at high concentrations, or cumulative doses may all be linked to undesirable outcomes. The reduction of glucocorticoid exposure while maintaining therapeutic efficacy is a priority in the present and future treatment of lupus nephritis.

References:

1. Heller NM, Curry S, Nickel R, Plunkett B, Huang S, Shyu A-B, Schleimer RP, Stellato C. Post-transcriptional regulation of eotaxin by glucocorticoids (GC) and by Interleukin (IL)-4. *J Allergy Clin Immunol* 2002; 109:S159.
2. Guhaniyogi J, Brewer G. Regulation of mRNA stability in mammalian cells. *Gene* 2001;265:11–23.
3. Wilusz CJ, Wormington M, Peltz SW. The cap-to-tail guide to mRNA turnover. *Nat Rev Mol Cell Biol* 2001;2:237–246.
4. Chen CY, Del Gatto-Konczak F, Wu Z, Karin M. Stabilization of interleukin-2 mRNA by the c-Jun NH2-terminal kinase pathway. *Science* 1998;280:1945–1949.
5. Poon M, Liu B, Taubman MB. Identification of a novel dexamethasone-sensitive RNA-destabilizing region on rat monocyte chemoattractant protein 1 mRNA. *Mol Cell Biol* 1999;19:6471–6478.
6. Chen CY, Shyu AB. AU-rich elements: characterization and importance in mRNA degradation. *Trends BiochemSci* 1995;20:465–470.
7. Bakheet T, Frevel M, Williams BR, Greer W, Khabar KS. ARED: human AU-rich element-containing mRNA database reveals an unexpectedly diverse functional repertoire of encoded proteins. *Nucleic Acids Res* 2001;29:246–254.
8. Fan XC, Steitz JA. Overexpression of HuR, a nuclear-cytoplasmic shuttling protein, increases the in vivo stability of ARE-containing mRNAs. *EMBO J* 1998;17:3448–3460.
9. Tebo J, Der S, Frevel M, Khabar KS, Williams BR, Hamilton TA. Heterogeneity in control of mRNA stability by AU-rich elements. *J BiolChem* 2003;278:12085–12093.
10.Hench PS, Kendall EC, Slocumb CH, Polley HF. Adrenocortical hormone in arthritis : preliminary report. Ann Rheum Dis. (1949) 8:97–104.doi: 10.1136/ard.8.2.97
11. Burns CM. The history of cortisone discovery and development. Rheum Dis Clin North Am. (2016) 42:1–14. doi: 10.1016/j.rdc.2015.08.001
12. Cameron JS. A Comparison of cortisone and prednisone in treatment of rheumatoid arthritis. Br Med J. (1957) 2:199–
202. doi: 10.1136/bmj.2.5038.199
13. Cameron JS. Lupus nephritis: an historical perspective 1968-1998. J Nephrol.(1999) 12(Suppl. 2):S29–41.
14. Pollak VE, Pirani CL, Schwartz FD.The natural history of the renal manifestations of systemic lupus erythematosus. 1964. J Am Soc Nephrol.(1997) 8:1189–98.
15. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids —New mechanisms for old drugs. N Engl J Med. (2005) 353:1711–
doi: 10.1056/NEJMra050541
16. Buttgereit F, Wehling M, Burmester G-R. A new hypothesis of modular glucocorticoid actions: steroid treatment of rheumatic diseases revisited. Arthritis Rheum.(1998) 41:761–73.doi: 10.1002/1529-0131(199805)41:5<761::AID-ART2>3.0.CO;2-M

17. Gaballa, S. A., Kompella, U. B., Elgarhy, O., Alqahtani, A. M., Pierscionek, B., Alany, R. G., & Abdelkader, H. (2021). Corticosteroids in ophthalmology: Drug delivery innovations, pharmacology, clinical applications, and future perspectives. Drug Delivery and Translational Research, 11, 866-893.
18. Kourakis, S., Timpani, C. A., Campelj, D. G., Hafner, P., Gueven, N., Fischer, D., &Rybalka, E. (2021). Standard of care versus new-wave corticosteroids in the treatment of Duchenne muscular dystrophy: Can we do better?. Orphanet Journal of Rare Diseases, 16(1), 1-9.
19. Russell, B., Moss, C., George, G., Santaolalla, A., Cope, A., Papa, S., & Van Hemelrijck, M. (2020). Associations between immune-suppressive and stimulating drugs and novel COVID-19—a systematic review of current evidence. ecancermedicalscience, 14.
20. Bruscoli, S., Febo, M., Riccardi, C., &Migliorati, G. (2021). Glucocorticoid therapy in inflammatory bowel disease: mechanisms and clinical practice. Frontiers in immunology, 12, 691480.