Journal of Applied Pharmaceutical Science Vol. 13(05), pp 023-032, May, 2023
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2023.90044
ISSN 2231-3354

Emerging corticosteroid resistance: Need for customized medication based on pharmacogenomics profiling

Navakanth Raju Ramayanam[1], Rajeshan Nanda Amarnath[2], Mohan Kumar Ramasamy[3], Thangavel Mahalingam Vijayakumar[1*]

[1]Department of Pharmacy Practice, SRM College of Pharmacy, SRM University, Chennai, India.
[2]Department of Medical Gastroenterology, SRM Medical College Hospital and Research Center, SRM University, Kanchipuram, India.
[3]Interdisciplinary Institute of Indian System of Medicine, SRM Institute of Technology and Sciences, SRM University, Chennai, India.

ARTICLE INFO

Received on: 27/11/2022
Accepted on: 25/03/2023
Available Online: 04/05/2023

Key words:
Corticosteroids, inflammatory diseases, pharmacogenetics, pharmacodynamics, personalized medicine, polymorphism.

ABSTRACT

Most of the prescribed drugs for inflammatory illnesses are corticosteroids. Since the majority of patients obtain maximum remission with corticosteroid treatment, glucocorticoids seem to have been the bedrock of treating inflammatory disorders for decades. The clinical signs of illness and harmful impacts of glucocorticoid therapy are presently most often standardized for the first manifestation and relapse of inflammatory disorders. Still, there is significant interindividual variance in the glucocorticoid treatment response. The principles of corticosteroids and the pharmacodynamics of steroids in diverse inflammatory disorders are discussed in this study. The significant interindividual heterogeneity in glucocorticoid response, however, need not be explained by these processes. Prior research has shown that genetic variables might significantly impact a patient's and dynamic pharmacokinetic characteristics. As a result, pharmacogenetics may play an important role in customized medication for individuals suffering from inflammatory illnesses. The significance of gene variants on glucocorticoid responsiveness and steroid-related hazards in inflammatory disorders is still unknown. Although the evidence is limited, the results of this research imply that pharmacogenetics may improve glucocorticoid therapy individualization. To make an overall conclusion on the genetic impact of variants on glucocorticoid related hazards and eventually adopt pharmacogenetics in medical practice, bigger cohorts of patients with inflammatory illnesses are required.

INTRODUCTION

According to the World Health Organization's step pyramid therapy for inflammatory diseases, corticosteroids are currently utilized to treat a wide range of inflammatory illnesses. Corticosteroids are also used to treat rheumatoid arthritis (RA), systemic lupus erythematosus, alcoholic hepatitis, asthma, chronic obstructive pulmonary disease, and other chronic inflammatory illnesses, although evidence for their usefulness in these cases is limited (Rainsford *et al*., 2015). Dexamethasone and other corticosteroids, such as prednisone, prednisolone, methyl prednisolone, and betamethasone, are routinely used to treat inflammatory conditions. Large interindividual variability in needs affects the usage of steroids, necessitating dose modifications to address issues such as insufficient therapeutic action or substantial side effects in patients (Liu *et al*., 2013). About 20%–30% of the patients treated with corticosteroids experience moderate side effects, and about 11% of them develop major side effects, such as gastrointestinal bleeding, peptic ulcers, and hypotension. Despite the lack of hard evidence, the issue of inadequate therapy even after corticosteroid use remains a significant clinical challenge (Narum *et al*., 2014). Genetic variables account for around 30%–70% of the interindividual variability in corticosteroid demand, according to animal studies and twin studies in humans. The variation in corticosteroid dose requirements has been linked to genetic polymorphisms in corticosteroid drug metabolizing enzymes, corticosteroid receptors, and inflammatory pathway components (Smolen *et al*., 2018). This review aims to highlight the detailed genetic features linked with corticosteroid resistance in order to identify variants that could be included in the application of a corticosteroid. For

*Corresponding Author
Thangavel Mahalingam Vijayakumar, Interdisciplinary Institute of Indian System of Medicine, SRM Institute of Technology and Sciences, SRM University, Chennai, India.
E-mail: vijaypractice @ yahoo.com

this review, we conducted a literature search in PubMed and Google Scholar using the following MESH terms: corticosteroids genetic polymorphism, resistance, and inflammatory illnesses. When the search was restricted to English from the beginning of February 2022, 290 articles were found.

CORTICOSTEROID RECEPTORS

The cytoplasmic glucocorticoid receptor (GR) is responsible for glucocorticoids'(GC) potential therapeutic effects. The GR could be a polymeric protein with three protein domains: the nontransactivation domain (NTD), DNA-binding domain (DBD), and ligand-binding domain (LBD) (Oakley and Cidlowski, 2013). Within the LBD and even at the DBD hinge region, two nuclear localization signals (NLSs) can be found. The NTD, which spans the GR's amino acids 1–420, is the most stable and thus the most variable domain of all nuclear receptors. A transcription activation function is present in the NTD that stimulates target genes without the use of ligands and serves as the primary site for all transcription factors (Ramamoorthy and Cidlowski, 2016). Among all the nuclear receptor proteins, the central DBD is well-preserved. Two of its zinc finger motifs engage glucocorticoid response element (GRE) and target DNA sequences in interactions. By combining 12 helices and 4 sheets, the hydrophobic ligand-binding pocket in the LBD is created. This carboxyterminal region contains a second activation function domain and sequences required for enabling ligand-dependent factor interactions (Duma *et al*., 2006).

Significant progress has been made in the gene regulation by which GCs function in recent years, and thus in the concept of such interpatient variability. Instead of being self-contained, the ligand-free GR is found in a heteromeric complex with molecular chaperones and co-chaperones in the cell. The cytoplasm contains GRs as 9S heteromeric complexes with minimal DNA binding. An heat shock protein 90 (Hsp90) dimer is linked to the receptor via protein–protein interactions within the hormone-binding domain with the "core" unit of an untransformed receptor. When GC bind to the cytosolic GR, they cause it to detach from Hsp90 and transition from a DNA-binding to a non-DNA-binding state in a temperature-dependent manner because the hormone causes the GR to separate from Hsp90 in intact cells and because the GR's interaction with Hsp90 corresponds to the hormone-inducible behavior of receptor mutants. The chaperone proteins identified in the heterocomplex include Hsp90, heat shock protein 70 (Hsp70), Hsp40, heat shock organizing protein, p23, and the immunophilins FKBP51 and FKBP.

In the biologically developed form of the heterocomplex, the free GR is attached to an Hsp90 dimer, p23, and any of the Hsp90 cochaperones besides Hsp70/Hsp90, a coordinating protein (Kirschke *et al*., 2014). Such interactions are necessary for maintaining the receptor's proper folding in a hormone-responsive state. When the receptors attach to ligands, the conformational changes reveal the DBD previously buried within the ligand-free conformation (de Iudicibus *et al*., 2011). NLSs are a densely packed arrangement of 588 basic amino acids localized within the DBD and engage with nuclear transport factors after being detected by cytosolic receptors (importins) (Beck *et al*., 2009). The movement of nuclear heterocomplexes is necessary for transactivating target genes. Nucleotide-binding complexes are thought to be used in ligand- and energy-dependent ways during translocation, which is a tightly regulated process. Nuclear transport regulators from the importin-12 family control it (Pemberton and Paschal, 2005). The nuclear membrane-to-GC-bound GR translocation was previously found to be significantly regulated by importin-13 (IPO13). The DBD's zinc finger motifs enable the functionalized receptor to interact directly with particular DNA sequences known as GC responsive elements (GREs, 5′-GGTACAnnnTGTTCT-3′ where *n* denotes any nucleotide), which are present in the promoter region of GC responsive genes (Reddy *et al*., 2009).

MOLECULAR MECHANISM OF CORTICOSTEROIDS

The GR is a transcriptional regulatory factor that homodimerizes on GR and promotes regulatory coactivators to a gene promoter. The GR regulates a variety of unique gene networks, each of which is dictated by certain cellular and physiological circumstances. cAMP response element-binding, CREB binding protein, steroid receptor coactivator 1, GR interacting protein, p300, and switching/sucrose nonfermenting chromatin remodeling complex (SWI/SNF) are examples of coactivators that initiate histone acetylation and allow the transactivation of GC responsive genes (Smith *et al*., 1996).

Transactivation primarily boosts the transcription of genes involved in physiological activities and is therefore to blame for the majority of adverse reactions, even though some of GC's anti-inflammatory effects are obtained by inducing anti-inflammatory genes like interleukin 10 and the inhibitor of nuclear factor kappa B (NF-κB) (Desmet and De Bosscher, 2017). Similar to how positive GREs drive transcriptional upregulation in response to GCs, negative GREs (5′-GGTACAnnnTGTTCT-3′) downregulate the reactive expression of genes. Therefore, the presence of GRs on GREs may prevent activator protein 1 (AP1) and NF-κB from binding to the same promoter regions or transactivating their respective inhibitory proteins. With the AP1, NF-κB, and transcription signal transducers and activators, the GRs physically interact. The majority of GC's anti-inflammatory effects are believed to be caused by transrepression (Xavier *et al*., 2016). Exogenous (therapeutic) GC differ from endogenous (physiologic) GC in several aspects; the most significant are their mineralocorticoid and glucocorticoid (anti-inflammatory) effects (Buttgereit *et al*., 2011) (Table 1). Philip S. Hench was the first to use biological cortisone to effectively treat people with atrophic arthritis in 1948 (Lipworth, 1999). In less than a year, Hench became aware of cortisone's mineralocorticoid-related side effects, such as sodium/water retention and potassium loss. As a result, throughout the 1950s and 1960s, novel therapeutic GC were produced. These medicines varied from the cortisone reported by Hench in that they had a lower mineralocorticoid action but much higher glucocorticoid active compounds (Samuel *et al*., 2017). Prednisone/prednisolone, methylprednisolone, and fluorinated GC like dexamethasone and betamethasone are among the most well tolerated and widely utilized of these medicines. Other differences between synthetic medications and natural GC include plasma dynamics, metabolism, biologic half-life, lipophilicity, and drug–receptor interactions (Kemp *et al*., 2016).

INTERINDIVIDUAL VARIABILITY OF CORTICOSTEROIDS

Individual variability in glucocorticoid receptivity is a significant barrier to glucocorticoid clinical applications, with up to 30% of the population displaying glucocorticoid resistance. According to developments in glucocorticoid expression patterns, impaired glucocorticoid response can be caused by increased expression of the glucocorticoid receptor β (GRB) and glucocorticoid receptor α (GRA) D isoforms, differences in GR phosphorylation, and homologously reduced the expression of GRs. Animal models with a similar pathophysiology to the human disease process under investigation must conduct preclinical investigations and novel drug tests efficiently. The effect of the GCs' genome has been studied in a variety of animal species. More than 95% of the human genome is shared by chimps, and they can be genetically changed to resemble specific human diseases. Additionally, it is possible to conduct trials that would be challenging on humans, while taking into account human variability (Bryda, 2013). The extent to which nonhuman models mimic human pathophysiology is unknown, despite the fact that glucocorticoid treatment in mouse models replicates some of the findings reported in humans (Hardy *et al*., 2018).

CORTICOSTEROIDS' BIOTRANSFORMATION

Corticosteroid metabolism is influenced by genetics. The genetic diversity seen in critical proteins along the route has a direct impact on a person's ability to metabolize drugs (Miller and Auchus, 2011). The cytochrome P450 (CYP) 3A enzyme family is responsible for the metabolism of GC like betamethasone (BMZ) and dexamethasone. One of the most commonly used inhaled GC for treating asthma is fluticasone propionate (FP), a trifluorinated synthetic glucocorticoid (Mager *et al*., 2003). This drug has a significant immunosuppressive effect, as demonstrated by the whole-blood lymphocyte proliferation assay. The metabolic biotransformation of FP, which is largely attributed to the CYP 3A enzymes CYP3A4, CYP3A5, and CYP3A7, ends the biological effects of FP. The most prevalent CYP3A isoform in the human lung is CYP3A5, but CYP3A4—possibly the most significant hepatic 3A enzyme—is only found in certain tissues. In the past, it has been demonstrated that substances can reduce the production of CYP3A4 in human lungs by binding to upstream gene regulatory domains of the CYP3A4 gene (Stockmann *et al*., 2013). CYP3A7, which was initially discovered to be expressed at low but detectable levels in lung samples from adults up to age 35, is possibly the most prevalent type of CYP3A expressed in the human fetal liver. Based on the upregulation of CYP3A5 and CYP3A7 in the bronchial mucosa and pulmonary parenchyma, our results suggest that these two enzymes are in charge of the local metabolization of FP in the lungs (Mager *et al*., 2003). Alterations in these CYP3A enzymes, which regulate corticosteroid biotransformation *in vivo*, could explain some of the variations in corticosteroid responses. The drug oxidation phenotypes of CYP3A4 are diverse yet consistently distributed. Nonetheless, there is significant proof of inheritance. In initial twin studies, the rate of antipyrine 4-hydroxylation, which is catalyzed predominantly by CYP3A4, was extremely hereditary (85%) (Klein and Zanger, 2013). A recurrent drug administration technique also indicated a high degree of inheritance for CYP3A4 drug oxidation capability for several of its targets (erythromycin: 89% and midazolam: 96%) (Teng, 2015).

A recent study identified the hereditary versus nongenetic influence on differential CYP3A4 induction using a traditional twin model technique. Although uninduced levels were not examined, it was reported that provoked CYP3A4 activity was about 66%, and that at least 20% of the variability was accounted for by environmental factors like BMI, alcohol consumption, and smoking habit/quantity (Rahmioglu *et al*., 2014). The CYP 3A enzyme breaks down prednisolone. Although CYP3A5 has a lower activity than CYP3A4, the two proteins have identical catalytic specificities (Floyd *et al*., 2003). The A6986G nucleotide polymorphism (SNP) inside intron 3 of CYP3A5, which is termed CYP3A5*3, correlates with CYP3A5 expression levels. The CYP3A5*3 mutant allele may also contribute to prednisolone pharmacokinetic variations between individuals (Zanger and Schwab, 2013).

Another possibly important gene is MDR1 (ABCB1), which codes for the transmembrane transporter p glycoprotein (Pg). The gene is involved in the metabolism of numerous xenobiotics and has been examined in relation to the susceptibility to Chron's disease (including steroids) (Table 2).

Numerous studies have focused on the two SNPs in the gene, C3435T (rs1045642), a synonymous SNP, and G2677T/A, a nonsynonymous triallelic variant (Krupoves *et al*., 2011). Researchers thought that IPO13 was a good biologic candidate gene for pharmacogenetics response to glucocorticoid therapy for asthma because of its established capacity to influence anti-inflammatory GC actions (especially in airway epithelium). To determine whether 10 common IPO13 DNA sequence variants affected the clinical outcome of inhaled corticosteroids (including budesonide, a commonly prescribed inhaled GC), researchers genotyped a group of asthmatic adolescents taking part in a clinical trial examining the long-term efficacy of inhaled anti-inflammatory therapy (Song *et al*., 2017) (Table 3).

PHARMACODYNAMICS

Due to increased secretion of the adrenocorticotrophic hormone (ACTH), mutations in the GR receptor cause disruption of hypothalamic–pituitary–adrenal (HPA) axis feedback mechanisms (reduced) and impaired function, leading to increased cortisol and mineralocorticoid output by the adrenal gland. On the other hand, if the GR gene is mutated, the cell would be more vulnerable to GC's actions. The mechanisms that determine a cell's susceptibility and resistance to GCs have remained unclear until now. In previous investigations, various polymorphisms in the GR gene have been associated with generalized sensitivity disorders. Single nucleotide polymorphisms (SNPs) in the GR pathway have been connected to therapeutic differences in corticosteroid response in a variety of inflammatory diseases. There is no proof, as far as researchers are aware, that SNP variations have an impact on pharmacogenetic end points (Kostik *et al*., 2011).

Glucocorticoid receptor

The GR, a member of the nuclear hormone receptor family of ligand-activated transcriptional activity, is the main target of GCs. The GR controls the transactivation or repression

Table1 . Salient molecular biological features of important genes involved in corticosteroid resistance.

Gene	Locus	Protein	Exons	Splice varient (or) isoform	Sub cellular localisation	Expression in tissues	Protein function
GR	5q31.3	NR3C1	16	12	Plasma membrane	Ubiquitous expression in fat, lung, and 25 other tissues	Receptor for GC. It has a dual-mode of action: as a transcription factor that binds to GRE, both for nuclear and mitochondrial DNA and as a modulator of other transcription factors. Affects inflammatory responses, cellular proliferation, and differentiation in target tissues. It is involved in chromatin remodelling (Kostik *et al*., 2011)
IL-4	5q31.1	IL-4	5	3	Plasma membrane	Expressed in the left adrenal gland and 207 other tissues	Receptor for both interleukin 4 and interleukin 13. Couples to the JAK1/2/3-STAT6 pathway. The IL4 response is involved in promoting Th2 differentiation. The IL4/IL13 responses are involved in regulating IgE production and chemokine and mucus production at sites of allergic inflammation (Kany *et al*., 2019)
Il-6	7p15.3	IL-6	6	N/A	Outside cell membrane	Expressed in the left coronary artery and 160 other tissues	Part of the receptor for interleukin -6. It binds to IL6 with low affinity but does not transduce a signal. Signal activation necessitates an association with IL6ST. Activation leads to the regulation of the immune response, acute-phase reactions, and hematopoiesis (Probable). The interaction with membrane-bound IL6R and IL6ST stimulates 'classic signaling', the restricted expression of the IL6R limits classic IL6 signaling to only a few tissues such as the liver and some cells of the immune system (Nilsson *et al*., 2005)
TNF-α	6p21.33	TNFA	4	5	Plasma membrane	Biased expression in bone marrow lymph node and 9 other tissues	Cytokine that binds to TNFRSF1A/TNFR1 and TNFRSF1B/TNFBR. It is mainly secreted by macrophages and can induce cell death of certain tumor cell lines. It is potent pyrogen causing fever by direct action or by stimulation of interleukin-1 secretion and is implicated in the induction of cachexia. Under certain conditions, it can stimulate cell proliferation and induce cell differentiation (Sreih *et al*., 2011)
MIF	22q11.23	MIF	3	3	Plasma membrane	Broad expression in kidney prostate and 21 other tissues	Pro-inflammatory cytokine. Involved in the innate immune response to bacterial pathogens. The expression of MIF at sites of inflammation suggests a role as a mediator in regulating the function of macrophages in host defense. Counteracts the anti-inflammatory activity of GC Serum levels of MIF are elevated in patients with severe sepsis or septic shock. High levels of MIF are correlated with low survival. Drugs that inhibit tautomerase activity protect against death due to sepsis.
CYT3A5	7q22.1	CYP family 3 Subfamily A Member 5	16	2	Membranes of endoplasmic reticulum	Liver and small intestine	A CYP monooxygenase is involved in the metabolism of steroid hormones and vitamins. Mechanistically, it uses molecular oxygen inserting one oxygen atom into a substrate and reducing the second into a water molecule, with two electrons provided by NADPH via CYP reductase (NADPH--hemoprotein reductase) (Miller and Auchus, 2011). Also involved in the oxidative metabolism of xenobiotics, including calcium channel blocking drug nifedipine and immunosuppressive drug cyclosporine (Stockmann *et al*., 2013)

Continued

Gene	Locus	Protein	Exons	Splice varient (or) isoform	Sub cellular localisation	Expression in tissues	Protein function
ABCB1	7q21.12	ATP-Binding Cassette Subfamily B Member 1	32	2	Plasma membrane	Liver, kidney, small intestine, and brain.	Translocates drugs and phospholipids across the membrane. Catalyzes the flop of phospholipids from the cytoplasmic to the exoplasmic leaflet of the apical membrane. Participates mainly in the flop of phosphatidylcholine, phosphatidylethanolamine, beta-D-glucosylceramides, and sphingomyelins (Zanger *et al*., 2013). Energy-dependent efflux pump responsible for decreased drug accumulation in multidrug-resistant cells (Krupoves *et al*., 2011)

Table 2. Salient molecular biological features of important SNPs involved in corticosteroid resistance.

SNP	Gene	DNA change (HGVS name)	Protein/Molecular-level changes
rs6189, rs6190	GR	774C>A, 772C>G	An *invivo* study indicated that ER22/23EK carriers are more "cortisol resistant" than non-carriers after receiving 1 md DEX, with better metabolic health profiles in cardiovascular patients and a higher survival rate (Huizenga *et al*., 1998)
rs10052957	GR	136G>A	In a study, NR3C1 rs10052957, a mild difference was observed in the association with steroid resistance between A allele and G allele carriers in nephrotic syndrome patients. The Tth111I polymorphism significantly modulated dexamethasone's effect on psychopathology outcome in cardiac surgery patients after dexamethasone administration (Kok *et al*., 2018)
rs6198	GR	056T>C	In a study modulating GC sensitivity may also have to do with variation in the clinical response to GCs in patients with RA or other inflammatory diseases (Kok *et al*., 2018)
rs2243250	IL-4	462C>G	According to a study, individual genetic factors will also affect the level of IL-4 in serum. Serum IgE level is used as a main long-term indicator to assess the severity of allergic diseases. It was reported that mice with impaired IL-4 haplotypes have significantly impaired specific IgE response to allergens (Zhang *et al*., 2016).
rs1800795	Il-6	026C>G	Regarding SNPs in interleukin 6 (IL6) gene, IL6 –174 (rs1800795) CC genotype and rs1800795 C allele were more frequent in Egyptian PV patients than controls from the same population. According to a study, polymorphisms in the promoter region of the IL-6 gene may be responsible for changes in the transcriptional activity and the expression of IL-6 in serum and synovial tissue, which could, in turn, lead to greater inflammation and thus affect the clinical status of RA patients.
rs1800629	TNF-α	254G>A	According to Albert *et al*., type 1 autoimmune hepatitis has a polymorphism rs1800629 for the TNF-A gene involving an A substitution at position -308 more commonly than normal individuals. This polymorphism can result in higher constitutive and inducible levels of TNF-A (Tanaka *et al*., 2014).
rs755622	MIF	205G>C	A meta-analysis showed that the gene polymorphism rs755622 plays an important role in the risk of glucocorticoid resistance in patients with nephrotic syndrome. Similar findings have been reported in glucocorticoid-resistant RA, systemic lupus erythematosus, and atherosclerosis. Polymorphisms of the MIF gene have been associated with glucocorticoid resistance in patients with RA and inflammatory bowel disease, although these findings have been disputed (Toldi *et al*., 2021)
rs776746	CYP3A5	916T>C	N/A
rs1045642	MDR1	329A>C	In a study candidate gene of interest is the MDR1 (ABCB1) gene that codes for Pg, a transmembrane transporter. The gene is involved in the metabolism of various xenobiotics (including steroids) and has been the subject of study for susceptibility to Chron's disease (Krupoves *et al*., 2011)

of GC-sensitive genes through protein interactions with other transcriptional regulators or direct DNA binding. The amplitude and effectiveness of the GC activity are influenced by the GR's characteristics. In Figure 1, the genetic variations in the GR are related to the reported GC reactivity heterogeneity. A binding assay was used to examine GCR expression in RA patients, mainly in peripheral mononuclear cells (Olsen *et al*., 2004).

It has been shown that GCR expression is downregulated in RA. Clinical evidence of steroid effect diminution, with long-term glucocorticoid medication, is uncommon, as the effect varies

Table3. Genetic polymorphism associated with corticosteroid resistance and its effects.

Gene	Molecule	Pathway	SNP	Genotype	Effect	References
GR	GR isoform alpha	Glucocorticoid receptor	rs6189	C>A	Glucocorticoid resistance, relative	El-Fayoumi *et al.* (2018).
GR	GR isoform alpha	Glucocorticoid receptor	rs6190	C>G	Glucocorticoid resistance, generalized	Quax *et al.* (2015).
GR	GR isoform alpha	Glucocorticoid receptor	rs10052957	G>A	Glucocorticoid resistance, generalized	Liu *et al.* (2018)
GR	GR isoform alpha	Glucocorticoid receptor	rs6198	T>C	Glucocorticoid resistance, generalized	Kok *et al.* (2018)
IL-4	Interleukin	Inflammatory pathway	rs2243250	C>G	N/A	Jiang *et al.* (2021)
Il-6	Interleukin	Inflammatory pathway	rs1800795	C>G	Risk-factor	Vitkauskaite *et al.* (2021)
TNF-α	Cytokine	Inflammatory pathway	rs1800629	G>A	Drug-response	Sreih *et al.* (2011)
MIF	Immune-regulatory cytokine	modulation of macrophages	rs755622	G>C	N/A	Toldi *et al.* (2021)
CYP3A5	CYP family 3 subfamily A member 5	Drug metabolism	rs776746	T>C	Drug-response	Klein and Zanger (2013)
ABCB1	ATP-Binding cassette subfamily B member 1	Drug metabolism	Rs1045642	T>G	Drug-response	Krupoves *et al.* (2011)

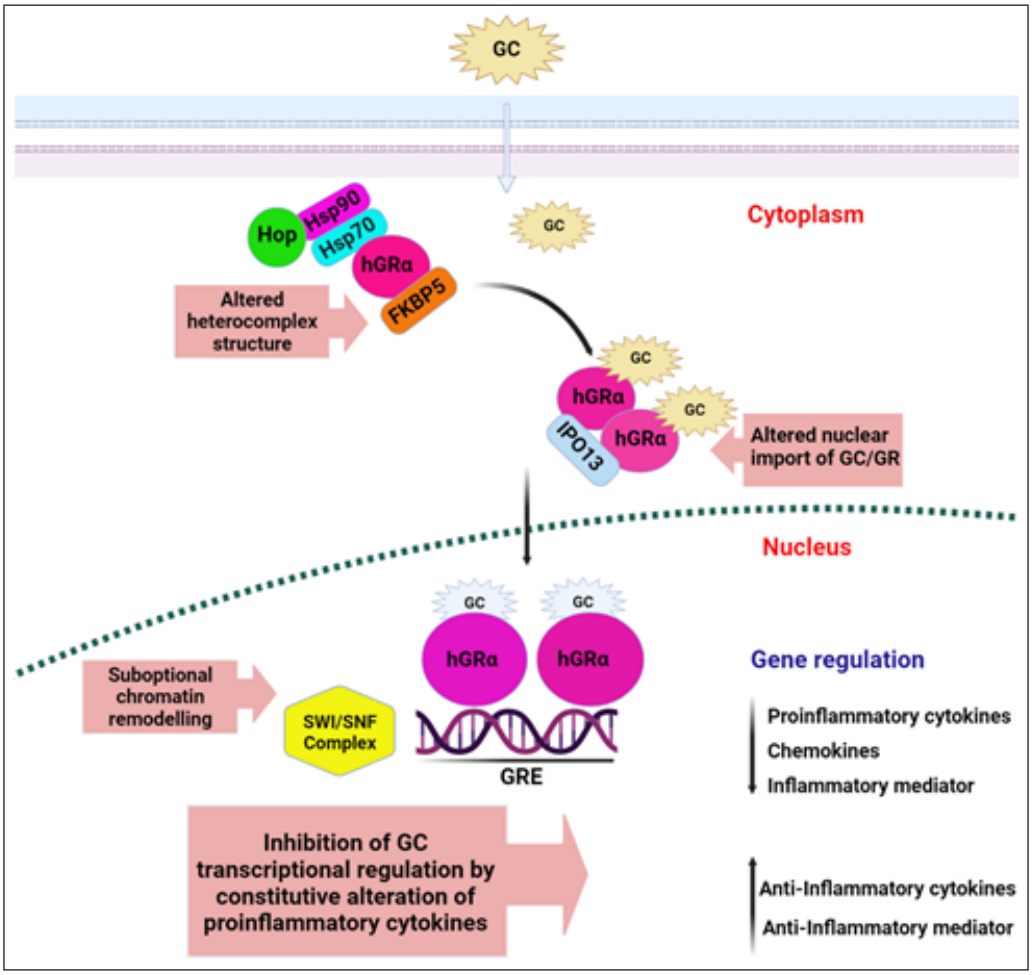

Figure 1. Molecular mechanism of corticosteroids.

from patient to patient. Exon 9beta (rs6198), TthIII1 (rs10052957), and ER22/23EK (rs6189&6190) polymorphisms in the GR gene have all been associated with varied degrees of resistance to exogenous GCs in patients with a variety of inflammatory diseases (Table 2).

Exon 2 of the GR gene contains the ER22/23EK polymorphism, which is located in the transcriptional region between codons 22 and 23. The particular sequence mutation is GAG AGG to GAA AAG, which translates glutamic acid arginine (ER) rs6189 to glutamic acid lysine (EK) rs6190. In prior investigations, the ER22/23 EK polymorphism was connected to GCs' resistance. The polymorphism ER22/23EK is linked to a reduced sensitivity to GCs. As a result, GRA performs better at translating than GRB, with the latter having a higher transactivating effect during transient transfection (El-Fayoumi *et al*., 2018). According to COS1 cell studies, the GC sensitivity of GR (ER22/23EK) carriers was reduced (Russcher *et al*., 2005). According to an *in vivo* study, ER22/23EK carriers have better metabolic health profiles in cardiovascular patients and a higher survival rate after receiving 1md DEX than noncarriers. They are also more "cortisol-resistant' than noncarriers.

A mutation known as Tth111I (rs10052957) has been found in the NR3C1 gene promoter. The SNP is located 3,807 bp above the exon's primary transcription start point in a 27-kb intron upstream of the transcription initiation site (between exons Ex1C and Ex1H) (Nicolaides *et al*., 2010). The gene promoter undergoes a C > T alteration as a result. In individuals with nephritic syndrome, NR3C1 rs10052957 revealed a little difference in steroid resistance between bearers of the A allele and the G allele (Liu *et al*., 2018). The Tth111I polymorphism dramatically altered the effect of corticosteroids on psychiatric outcomes in heart surgery patients after dexamethasone administration (Kok *et al*., 2018).

The 9beta (rs6198) SNP, an adenine to guanine nucleotide substitution in the GR gene, is located in the GR9 region. The G allele of this polymorphism results in a more stable GR9 mRNA and increased GR9 isoform receptor protein synthesis, which may be related to GC resistance, according to *in vitro* findings (Castro-Vale *et al*., 2021). An ATTTA pattern symbolizes the shift from A to G in the nucleotide (to GTTTA). The ATTTA motif is considered to interfere with mRNA and restrict the *in vitro* synthesis of receptor proteins. It has been discovered that the GR9beta transcript variation is a dominant-negative GR inhibitor. According to *in vitro* research, the GR9beta polymorphism increases sustained GR mRNA levels and may also increase GC resistance. Furthermore, GR9beta has been associated to increased vulnerability to RA and decreased resistance to *Staphylococcus aureus* nasal colonization, suggesting an immune system function mediated by GR (Van Winsen *et al*., 2009). In certain inflammatory disorders, the increased expression of the GR9 protein variation has been linked to GC resistance.

A recent study found that healthy male carriers of the 9beta variation exhibited higher overall cortisol responses following social stress and higher ACTH levels after a dexamethasone suppression test (0.25 mg), suggesting GC insensitivity at the level of the HPA axis. The involvement of the polymorphisms ER22/23EK (rs6189, rs6190), Tth111I (rs10052957), and GR beta 9 (rs6198) in responding to corticosteroids in a number of illnesses has not received much attention. A Tth111I polymorphism in the NR3C1 gene was found to be connected to the pathophysiology of chronic bronchitis, which causes asthma. On the other hand, alterations of GC sensitivity by 9 and ER22/23EK may be linked to variations in the clinical response to GCs in individuals with RA or other inflammatory disorders (Pratt *et al*., 1992). The ER22/23EK polymorphism, one of the three polymorphisms previously discussed, has been associated by numerous researchers with corticosteroid resistance in the majority of inflammatory illnesses.

GR heterocomplex

The absence of the activation of the GR heterocomplex may be attributed to defects in gene expression. Barnes (2010) found that after glucocorticoid administration, patients with glucocorticoid-resistant asthma exhibited less transactivation of GR and decreased GRE binding in PBMCs, which could be attributable to GR phosphorylation. Inconsistencies in the chaperones and co-chaperones that make up the mature GR heterocomplex, which is necessary for accurate ligand binding and increased expression of the regulatory response, may lead to reduced corticosteroid responsiveness. Kojika's studies showed a relationship between altered Hsp90 and Hsp70 and reduced cellular sensitivity. All 97 Chinese patients who met the updated 2017 McDonald criteria for MS or clinically isolated syndrome were included in the study (Barnes, 2010; Ramamoorthy and Cidlowski, 2016).

Patients were given glucocorticoid impulse therapy (methylprednisolone 500 mg/day for 5 days) while they were experiencing an acute attack. One of these is a study of the variations in GR and FKBP5 levels between GC responders and nonresponders, and its goal is to see whether there are any viable means of modifying glucocorticoid reactivity. The study discovered that GR levels were higher in GC-sensitive patients but lower in FKBP5 patients, suggesting that decreasing FKBP5 could increase the effectiveness of GC in GC-resistant patients (Table 3). The mediators are both anti- and pro-inflammatory. Unknown are the precise pathophysiological processes behind glucocorticoid resistance (Song *et al*., 2020).

One theory holds that the modulatory imbalance between T helper subtype 1 (Th1) and T helper subtype 2 (Th2) cells is related to corticosteroid resistance. The association between genetic variations in the IL4, IL6, TNF, and genes has been investigated in a number of studies, including those of individuals with a variety of illnesses. However, there is little proof that people with inflammatory illnesses have genetic variations in cytokine genes (Kany *et al*., 2019).

IL-4

Mast cells, B lymphocytes, activated Th2 cell subsets, and other immune cells all release the pleiotropic cytokine IL-4. Basophils, mast cells, B lymphocytes, activated Th2 cell subsets, and other inflammatory cells also release the pleiotropic cytokine IL-4. It has a significant role in the immunological response of Th2 cells. IL-4 can boost humoral immunity while reducing the impact of Th1 cytokines (IFN, IL1, and so on). The body's IL-4 concentration significantly rises as a result of inflammatory diseases.

According to a study, unique genetic traits can change the level of IL-4 in the serum. The severity of allergic illnesses can be predicted over time by looking at serum IgE levels. Specific IgE responses to allergens were considerably reduced in mice with defective IL-4 haplotypes. The majority of research (Table 3) (Zhang *et al*., 2016) associates the IL-4 rs2243250 locus, allele T, and genotype TT with an elevated risk of corticosteroid resistance (Table 3). The sensitivity analysis supported the consistency of the findings in the homozygous genetic model, even though there was substantial instability in the allele and recessive gene models. Therefore, it is important to take into account the finding that having the allele T increases one's risk of developing corticosteroid resistance.

IL-6

In addition to fibroblasts, T and B lymphocytes, and vascular endothelial cells, mononuclear phagocytes produce the majority of the multifunctional bioactive peptide interleukin 6 (IL-6). The human IL-6 gene has a total length of 5 kb, 4 introns, and 5 exons, and is found on chromosome 7p21-14 (Nilsson *et al*., 2005). The rs1800795 polymorphism in the promoter of the coding gene IL-6 can change cytokine production by affecting gene transcription. This SNP has thus been examined in earlier research on a range of inflammatory diseases.

Blood IL-6 levels have been found to be impacted by the rs1800795 polymorphism in the promoter of the IL-6 coding gene. When it came to SNPs in the interleukin-6 (IL-6) gene, it was found that Egyptian PV patients were more likely to have the IL-6-174 (rs1800795) CC genotype and the rs1800795 C allele than controls from the same population. According to a study, IL-6 may be responsible for differences in transcriptional regulation and production in serum and synovial tissue, which may lead to increased inflammation and thus alter the patient's condition (Vitkauskaite *et al*., 2021). The CC genotype (60.8%) was similar to the genotype allocation of the controls, in contrast to the most common genotype in numerous pathological conditions (Tanaka *et al*., 2014).

TNF-α

TNF is another important pro-inflammatory cytokine that plays a role in the inflammatory process. TNF levels have been observed to be elevated in the plasma and urine of people suffering from inflammatory disorders. The significance of SNPs in the gene encoding TNF in individuals with inflammatory illnesses has been studied, although the outcomes have been mixed (Sreih *et al*., 2011). The type 1 autoimmune hepatitis has a polymorphism rs1800629 for the TNF-α gene with an α substitution at position 308, which is more frequent in comparison to healthy people. TNF-α levels can be increased both constitutively and inducibly as a consequence of this polymorphism.

This polymorphism has been linked to an increased recurrence of treatment failure, disease progression, and mortality in malignancies, such as non-Hodgkin's lymphoma, as well as a reduction in the clearance of infectious agents that cause diseases like malaria and mucocutaneous leishmaniasis, as well as a greater tendency for immune disorders like systemic LE and RA (Parameswaran and Patial, 2010). However, more patients should be included in the study, as well as blood and tissue TNF-α levels.

Macrophage migration inhibitory factor (MIF)

MIF, a cytokine that promotes inflammation and has antiglucocorticoid activity, has been associated with a variety of inflammatory diseases (Parameswaran and Patial, 2010). GC activate a protein called MIF, which prevents MKP1 from being induced and mutes its anti-inflammatory effects. Patients with ulcerative colitis who are glucocorticoid-resistant have colonic mononuclear cells with higher MIF expression, and an anti-MIF antibody restores the anti-inflammatory response to GC in these cells. A meta-analysis found that the gene polymorphism rs755622 significantly affects the prevalence of glucocorticoid resistance in individuals with nephrosis (Table 3).

Identical results are found in glucocorticoid-resistant systemic lupus erythematosus, atrophic arthritis, and atherosclerosis. Glucocorticoid resistance is associated with mutations in the MIF gene in patients with inflammatory bowel disease and atrophic arthritis, despite these findings being contested (Table 2). According to the hypothesis, a GC mutation in the MIF gene at 173 bp raises MIF levels in the blood, promoting a pro-inflammatory response, podocyte destruction, and worsening the severity of inflammation (Table 3). MIF has also been linked to glucocorticoid resistance in patients with asthma and acute respiratory distress syndrome. Anti-MIF medications may thus be useful in a variety of glucocorticoid-resistant illnesses.

CONCLUSION

In medical practice, GCs are the most commonly used treatment for a variety of illnesses, including immunosuppressive and anti-inflammatory medications. The effects of GCs are mediated by a plethora of nongenomic and genomic pathways, most notably gene transcription control. By interacting with the GR, GCs control the transcription of some target genes. In the scoping research, we aimed to characterize the key genes and SNPs that may cause glucocorticoid resistance and the molecular mechanisms of anti-inflammatory effects, which could be useful in creating newer pharmaceutical alternatives for undoing GC resistance.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

FINANCIAL SUPPORT

There is no funding to report.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

PUBLISHER'S NOTE

This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

REFERENCES

Barnes PJ. Mechanisms and resistance in glucocorticoid control of inflammation. J Steroid Biochem Mol Biol, 2010; 120:76–85.

Beck IME, Berghe W Vanden, Vermeulen L, Yamamoto KR, Haegeman G, De Bosscher K. Crosstalk in inflammation: the interplay of glucocorticoid receptor-based mechanisms and kinases and phosphatases. Endocr Rev, 2009; 30:830–82.

Bryda EC. The mighty mouse: the impact of rodents on advances in biomedical research. Mo Med, 2013; 110(3):207–11.

Buttgereit F, Burmester GR, Straub RH, Seibel MJ, Zhou H. Exogenous and endogenous glucocorticoids in rheumatic diseases. Arthritis Rheum, 2011; 63:1–9.

Castro-Vale I, Durães C, van Rossum EFC, Staufenbiel SM, Severo M, Lemos MC, Carvalho D. The glucocorticoid receptor gene (Nr3c1) 9β snp is associated with posttraumatic stress disorder. Healthcare, 2021; 9:1–11.

de Iudicibus S, Franca R, Martelossi S, Ventura A, Decorti G. Molecular mechanism of glucocorticoid resistance in inflammatory bowel disease. World J Gastroenterol, 2011; 17:1095–108.

Desmet SJ, De Bosscher K. Glucocorticoid receptors: finding the middle ground. J Clin Invest, 2017; 127:1136–45.

Duma D, Jewell CM, Cidlowski JA. Multiple glucocorticoid receptor isoforms and mechanisms of post-translational modification. J Steroid Biochem Mol Biol, 2006; 102:11–21.

El-Fayoumi R, Hagras M, Abozenadaha A, Bawazir W, Shinawi T. Association between NR3C1 gene polymorphisms and toxicity induced by glucocorticoids therapy in Saudi children with acute lymphoblastic leukemia. Asian Pac J Cancer Prev, 2018; 19:1415–23.

Floyd MD, Gervasini G, Masica AL, Mayo G, George AL, Bhat K, Kim RB, Wilkinson GR. Genotype-phenotype associations for common CYP3A4 and CYP3A5 variants in the basal and induced metabolism of midazolam in European- and African-American men and women. Pharmacogenetics, 2003; 13:595–606.

Hardy RS, Zhou H, Seibel MJ, Cooper MS. Glucocorticoids and bone: consequences of endogenous and exogenous excess and replacement therapy. Endocr Rev, 2018; 39:519–48.

Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease. Int J Mol Sci, 2019; 20:1–31.

Kemp MW, Newnham JP, Challis JG, Jobe AH, Stock SJ. The clinical use of corticosteroids in pregnancy. Hum Reprod Update, 2016; 22:240–59.

Kirschke E, Goswami D, Southworth D, Griffin PR, Agard DA. Glucocorticoid receptor function regulated by coordinated action of the Hsp90 and Hsp70 chaperone cycles. Cell, 2014; 157:1685–97.

Klein K, Zanger UM. Pharmacogenomics of cytochrome P450 3A4: recent progress toward the "missing heritability" problem. Front Genet, 2013; 4:1–15.

Kok L, Hillegers MH, Veldhuijzen DS, Boks MP, Dieleman JM, van Dijk D, Joëls M, Vinkers CH. Genetic variation in the glucocorticoid receptor and psychopathology after dexamethasone administration in cardiac surgery patients. J Psychiatr Res, 2018; 103:167–72.

Kostik MM, Klyushina AA, Moskalenko MV, Scheplyagina LA, Larionova VI. Glucocorticoid receptor gene polymorphism and juvenile idiopathic arthritis. Pediatr Rheumatol, 2011; 9:1–7.

Krupoves A, MacK D, Seidman E, Deslandres C, Amre D. Associations between variants in the ABCB1 (MDR1) gene and corticosteroid dependence in children with Crohn's disease. Inflamm Bowel Dis, 2011; 17:2308–17.

Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. Arch Intern Med, 1999; 159:941–55.

Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, Brown JP, Cohen A, Kim H. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol, 2013; 9(1):1–25.

Liu J, Wan Z, Song Q, Li Z, He Y, Tang Y, Xie W, Xie Y, Zhang J. NR3C1 gene polymorphisms are associated with steroid resistance in patients with primary nephrotic syndrome. Pharmacogenomics, 2018; 19:45–60.

Mager DE, Moledina N, Jusko WJ. Relative immunosuppressive potency of therapeutic corticosteroids measured by whole blood lymphocyte proliferation. J Pharm Sci, 2003; 92:1521–5.

Miller WL, Auchus RJ. The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. Endocr Rev, 2011; 32:81–151.

Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ Open, 2014; 4:1–10.

Nicolaides C, Galata Z, Kino T, Chrousos GP, Charmandari E. The human glucocorticoid receptor: molecular basis of biologic function. Steriods, 2010; 75:1–28.

Nilsson MB, Langley RR, Fidler IJ. Interleukin-6, secreted by human ovarian carcinoma cells, is a potent proangiogenic cytokine. Cancer Res, 2005; 65:10794–800.

Oakley RH, Cidlowski JA. The biology of the glucocorticoid receptor: new signaling mechanisms in health and disease. J Allergy Clin Immunol, 2013; 132:1033–44.

Olsen NJ, Moore JH, Aune TM. Gene expression signatures for autoimmune disease in peripheral blood mononuclear cells. Arthritis Res Ther, 2004; 6:120–8.

Parameswaran N, Patial S. Tumor necrosis factor-a signaling in macrophages. Crit Rev Eukaryot Gene Expr, 2010; 20:87–103.

Pemberton LF, Paschal BM. Mechanisms of receptor-mediated nuclear import and nuclear export. Traffic, 2005; 6:187–98.

Pratt WB, Scherrer LC, Hutchison KA, Dalman FC. A model of glucocorticoid receptor unfolding and stabilization by a heat shock protein complex. J Steroid Biochem Mol Biol, 1992; 41:223–9.

Rahmioglu N, Nyholt DR, Morris AP, Missmer SA, Montgomery GW, Zondervan KT. Genetic variants underlying risk of endometriosis: insights from meta-analysis of eight genome-wide association and replication datasets. Hum Reprod Update, 2014; 20(5):702–16.

Rainsford KD, Parke AL, Clifford-Rashotte M, Kean WF. Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. Inflammopharmacology, 2015; 23:231–69.

Ramamoorthy S, Cidlowski JA. Corticosteroids: mechanisms of action in health and disease. Rheum Dis Clin North Am, 2016; 42:15–31.

Reddy TE, Pauli F, Sprouse RO, Neff NF, Newberry KM, Garabedian MJ, Myers RM. Genomic determination of the glucocorticoid response reveals unexpected mechanisms of gene regulation. Genome Res, 2009; 19:2163–71.

Russcher H, Smit P, Van Den Akker ELT, Van Rossum EFC, Brinkmann AO, De Jong FH, Lamberts SWJ, Koper JW. Two polymorphisms in the glucocorticoid receptor gene directly affect glucocorticoid-regulated gene expression. J Clin Endocrinol Metab, 2005; 90:5804–10.

Samuel S, Nguyen T, Choi HA. Pharmacologic characteristics of corticosteroids. J Neurocritical Care, 2017; 10:53–9.

Smith CL, Oñate SA, Tsai MJ, O'Malley BW. CREB binding protein acts synergistically with steroid receptor coactivator-1 to enhance steroid receptor-dependent transcription. Proc Natl Acad Sci U S A, 1996; 93:8884–8.

Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, Kavanaugh A, McInnes IB, Solomon DH, Strand V, Yamamoto K. Rheumatoid arthritis. Nat Rev Dis Prim, 2018; 4:1–23.

Song Q, Tang Y, Liu J. Pharmacogenomics genetic variation in the glucocorticoid. Pharmacogenomics, 2017; 18:293–316.

Song T, Chang H, Du L, Yin L, Shi F, Zhang X. Glucocorticoid receptor mutations and clinical sensitivity to glucocorticoid in Chinese multiple sclerosis patients. Neurol Sci, 2020; 41:2767–71.

Sreih A, Ezzeddine R, Leng L, Lachance A, Yu G, Mizue Y, Subrahmanyan L, Pons-Estel BA, Abelson AK, Gunnarsson I, Svenungsson E, Cavett J, Glenn S, Zhang L, Montgomery R, Perl A, Salmon J, Alarcón-Riquelme ME, Harley JB, Bucala R. Dual effect of the macrophage migration inhibitory factor gene on the development and severity of human systemic lupus erythematosus. Arthritis Rheum, 2011; 63:3942–51.

Stockmann C, Fassl B, Gaedigk R, Nkoy F, Uchida DA, Monson S, Reilly CA, Leeder JS, Yost GS, Ward RM. Fluticasone propionate pharmacogenetics: CYP3A4*22 polymorphism and pediatric asthma control. J Pediatr, 2013; 162(6):162.

Tanaka T, Narazaki M, Kishimoto T. Il-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol, 2014; 6:a016295.

Teng R. Ticagrelor: pharmacokinetic, pharmacodynamic and pharmacogenetic profile: an update. Clin Pharmacokinet, 2015; 54(11):25–38.

Van Winsen LML, Manenschijn L, Van Rossum EFC, Crusius BA, Koper JW, Polman CH, Uitdehaag BMJ. A glucocorticoid receptor gene haplotype (TthIII1/ER22/23EK/9β) is associated with a more aggressive disease course in multiple sclerosis. J Clin Endocrinol Metab, 2009; 94:2110–4.

Vitkauskaite A, Celiesiute J, Juseviciute V, Jariene K, Skrodeniene E, Samuolyte G, Nadisauskiene RJ, Vaitkiene D. IL-6 597A/G (rs1800797) and 174G/C (rs1800795) gene polymorphisms in the development of cervical cancer in Lithuanian Women. Medicina (B Aires), 2021; 57:1025.

Xavier AM, Anunciato AKO, Rosenstock TR, Glezer I. Gene expression control by glucocorticoid receptors during innate immune responses. Front Endocrinol (Lausanne), 2016; 7:1–8.

Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther, 2013; 138:103–41.

Zhang Z, Wang L, Sun X, Zhang L, Lu L. Association of IL4 and IL4R polymorphisms with multiple sclerosis susceptibility in Caucasian population: a meta-analysis. J Neurol Sci, 2016; 363:107–13.

How to cite this article:
Ramayanam NR, Amarnath RN, Ramasamy MK, VijayakumarTM. Emerging corticosteroid resistance: Need for customized medication based on pharmacogenomics profiling. J Appl Pharm Sci, 2023; 13(05):023–032.