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REVIEW

Pharmacogenomic Response of Inhaled Corticosteroids for the Treatment of Asthma: Considerations for Therapy

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Abstract: There is a large interindividual variability in response to ICSs in asthma. About 70% of the variance in ICS response is likely due at least partially to genetically determined characteristics of target genes. In this article, we examine the effects on the ICS response of gene variations in the corticosteroid pathway, and in the pharmacokinetics of corticosteroids, and also those outside the corticosteroid pathway, which have the potential to influence corticosteroid activity. Although the available evidence indicates that responses to ICSs in asthma are influenced by different genetic variants, there are still deep uncertainties as to whether a real association between these genetic variants and corticosteroid response could also possibly exist because there are difficulties in reproducing pharmacogenetic findings. This explains at least partly the insufficient use of pharmacogenomic data when treating asthmatic patients, which creates a real limitation to the proper use of ICSs in an era of precision medicine that links the right patient to the right treatment. Knowing and dealing with the genetic factors that influence the therapeutic ICS response is a fundamental condition for prescribing the right dose of ICS to the right patient at the right time.

Keywords: asthma, inhaled corticosteroids, gene polymorphisms, genome-wide association studies, precision medicine

Introduction

Inhaled corticosteroids (ICSs) are the mainstay of treatment for asthma, but are also characterized by highly variable interindividual responses among asthmatic patients, with some subjects in whom the expected therapeutic effect is not achieved, while others exhibit even severe adverse reaction and the majority show intermediate responses between the above two extreme cases.[1] This between-person variability is the result of disparate causes such as disease severity, treatment compliance, concurrent illnesses, environmental and infection exposures, age, medicinal product interactions, and also the definition of response (improved lung function vs persisting symptoms vs exacerbation).[1,2] However, a key role in determining interindividual variability in response to ICS seems to be played mainly by the characteristics of target genes or drug metabolizing enzymes that are under genetic influence.[1,3]

ICSs work by binding to the intracellular glucocorticoid receptor (GR), which is encoded by the nine-exon gene NR3C1,[4] followed by translocation to the nucleus and binding to its cognate DNA sequences called glucocorticoid response elements (GREs), mediating the transcriptional activities of a wide variety of genes. Their anti-inflammatory

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activity is achieved through a combination of inhibition, the so-called "transrepression", and upregulation, or "transactivation", of gene transcription.[5] The transrepression results in a reduced production of pro-inflammatory cytokines, and is due to an inhibition of genes regulating expression of many pro-inflammatory cytokines, such as interleukin (IL)-1, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, tumor necrosis factor-α (TNF-α), granulocyte–macrophage colony-stimulating factor (GM-CSF), interferon-γ (IFN-γ),[4] and also that of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2).[6] Alternatively, GR interferes with the activation and/or activity of other DNA-related transcription factors, mainly nuclear factor (NF)-κB, and activating protein (AP)-1, but also cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), interferon regulatory factor 3 (IRF3), nuclear factor of activated T-cells (NFAT), signal transducer and activator of transcription (STAT), T-box expressed in T-cells (T-Bet), and GATA-3, rather than directly binding to DNA.[7] In any case, it influences gene regulation.[7]

The transactivation results in an augmented synthesis of anti-inflammatory proteins with an upregulated expression of annexin A1, previously named lipocortin-1, which produces a direct inhibition of phospholipase A2 (PLA2) that causes a reduced prostaglandin and leukotriene production,[8] an inhibition of COX-2 that occurs in a post-transcriptional manner,[9] a detachment of neutrophil from the endothelium, and a reduction in neutrophil penetration through the endothelium of blood vessels.[8] Furthermore, some genes that encode anti-inflammatory proteins such as inhibitor of NF-κB (IκB-α), secretory leukoprotease inhibitor, glucocorticoid-induced leucine zipper protein (GILZ), and mitogen activated kinase phosphatase-1 are induced through transactivation.[10] Apparently, transactivation plays a critical role in the onset of unwanted adverse events induced by ICSs.[11]

About 70% of the variability in ICS response is likely due to individual characteristics of target genes.[12] However, there is still notable uncertainty whether a real association between genetic variants and corticosteroid response could exist. In fact, the effects of gene variations in the corticosteroid pathway on the response to ICS therapy are often under discussion due to the frequent lack of reduplicate results.[13] This is a big issue. In fact, understanding the impact of these gene variations on the response to ICSs could likely lead to identification of genetic markers that predict if an ICS treatment will work. These biomarkers would allow a personalized treatment of patients with asthma and, accordingly, a better quality of care.[14]

In this article, we will examine the effects on ICS response of corticosteroid pathway gene variations, those of genetic variation in the pharmacokinetics of corticosteroids, and also those of gene variations outside of the corticosteroid pathway that have the potential to influence the corticosteroid activity (Table 1). The information given, when not otherwise noted, refers to studies conducted in humans.

Corticosteroid Pathway Gene Variation

CRHR1 Gene Polymorphisms

Corticotrophin-releasing hormone (CRH) binds to CRH receptor 1 (CRHR1) in the pituitary gland and modulates the release of adrenocorticotropic hormone, which induces cortisol production and regulates endogenous corticosteroid levels. *CRHR1*, which maps on chromosome 17q12-q22, encodes for CRHR1.[15] Variations in this gene could alter the response to ICS by influencing the level of endogenous corticosteroid secretion, with lower levels eliciting a better response to exogenous corticosteroids.[16] However, available data are inconclusive so far.

Several intronic single nucleotide polymorphisms (SNP) in this gene have been studied. The rs242941 and rs1876828 polymorphisms of the *CRHR1* gene seem to be correlated with a good response to ICSs.[17] Greater increases in lung function in response to corticosteroids have been correlated with the presence of the rs242941 polymorphism.[18,19] However, it was also reported that rs242941, but not rs1876828, is associated with a negative ΔFEV_1%pred compared to major allele homozygotes and heterozygotes.[20] Another two studies were unable to document any FEV_1 improvement after ICSs treatment in the presence of these two polymorphisms.[21,22]

NR3C1 GR Gene Polymorphisms

The nuclear receptor subfamily 3 group C member 1 (*NR3C1*), which is located on chromosome 5q31–q32 and consists of nine exons, is the only known GR gene. It encodes the GR producing mRNA, which constitutes the basis for GR isoforms (GRα, GRβ, GRγ, and GRδ). Only GRα is active, whereas GRβ inhibits the signal pathway of GRα and induces an impaired sensitivity to corticosteroids,[23] while the functions GRγ and GRδ, which are post-transcriptional modifications of the *NR3C1* gene, are still under investigation.[24] The GRα and GRβ isoforms have been subdivided into eight GRα and eight GRβ isoforms that have different post-translational

Table 1 Polymorphisms That Influence the Response of ICSs

Gene	Associated Loci	Response Phenotype	Reference
Corticosteroid pathway gene variations			
CRHR1	rs242941 rs1876828	Greater increases in lung function in response to corticosteroids	[17,19]
	rs242941	Associated with a negative $\Delta FEV_{1\%}$ predicted compared to major allele homozygotes and heterozygotes	[20]
NR3C1	ER22/23EK (rs6189 and rs6190)	Significant reduction of transactivating capacity of GRα	[30]
	*Bcl*I (rs41423247)	A higher improvement in FEV_1 at 4 hours with high-dose ICS	[22]
		Corticosteroid resistance	[32]
	N363S (rs6195)	Associated with an increase in corticosteroid sensitivity	[33]
	*TthIII*I (rs10052957)	Associated with corticosteroid resistance	[26,35]
STIP1	rs6591838 rs223647 rs6591838 rs1011219	Greater increases in lung function in response to corticosteroids, with the biggest change observed with rs6591838	[41]
FKBP4	rs4713916	Correlated with corticosteroid resistance at least in Crohn's disease	[43]
DUSP1	rs881152 rs34507926	Associated with greater bronchodilator responses and better asthma control in patients under regular ICS treatment	[49]
HDAC1	rs1741981	Significantly associated with a smaller improvement in FEV_1 in response to corticosteroid therapy in asthmatics	[54]
HDAC2	rs58677352	No relationship with possible changes in pulmonary function induced by corticosteroids	[54]
Genetic variation in the pharmacokinetics of corticosteroids			
CYP3A	*CYP3A4*22* (rs35599367)	Associated with a significant improvement in asthma control scores in patients receiving fluticasone propionate	[57]
	*CYP3A5*3* (rs776746)	Related to asthma control scores in subjects under inhaled beclomethasone treatment	[58]
MDR1 (*ABCB1*)	C1236T (rs1128503) G2677T/A (rs2032582) C3435T (rs1045642)	The initial steroid response in children with nephrotic syndrome may be influenced by genetic variations in *MDR1*	[16,60]
IPO13		Genetic variation in *IPO13* is associated with reduced airway hyperresponsiveness among children with mild-to-moderate asthma who are not using long-term ICSs	[65]
Other genetic variations that can modify the corticosteroid activity			
NR1I2	rs3842689	Associated with unresponsiveness to corticosteroids	[66]
TBX21	rs2240017	Improvement in bronchial hyperresponsiveness or better bronchoprotection during ICS treatment	[67]
GLCCI1	rs37972	Significant association with a decreased response to ICS therapy in asthmatic patients	[68]
FBXL7	rs10044254	Associated with improved symptomatic response to ICSs only in children	[72]
ORMDL3	rs2872507 rs72821893	Associated with ICSs treatment response in atopic subjects	[74,75]

(*Continued*)

Table 1 (Continued).

Gene	Associated Loci	Response Phenotype	Reference
VEGFA	rs2146323	Associated with response to ICS therapy in asthma patients	[77]
BBS9	rs2392165	Significant association with ICS use when treating wheezing/coughing, with better ICS response	[80]
FCER2	T2206C (rs28364072)	It can predict low-response to ICS in childhood asthma	[81,82]

modifications.[25] It is likely that differential expression in various cell types might explain distinct cellular responsiveness. Within the cell, GRα cannot move into the cell nucleus because it is part of a large multiprotein complex that includes chaperone proteins (heat shock protein [HSP] 90, HSP70 and p23) and immunophilins (binding protein FK506 [FKBP] 51 and FKBP52). However, when GRα binds to the corticosteroid, it dissociates from the multiprotein complex through hyperphosphorylation and migrates to the nucleus, where it binds to the GRE.

Polymorphisms of *NR3C1* cause modifications of the secondary and tertiary domain structures in the GR, and disturb transcription initiation and stability of the mRNA for the GR.[26] Although many polymorphisms of this gene have been identified, we still do not know if and how really all these GR variants influence the responses to ICSs.[27] In general, mutations in *NR3C1* are associated with corticosteroid resistance, although some GR polymorphisms are associated with function improvements.[13] They may not only inhibit the formation of the GR/corticosteroid complexes, but also reduce transcription and cause transrepression of genes that encode protein synthesis within the framework of cell response to corticosteroids. Thus, they reduce GR expression which, compromised in its structure and function, elicits a weaker response to corticosteroids.[28]

ER22/23EK, N363S, and *Bcl*I are the common polymorphisms of *NR3C1* that influence corticosteroid treatment.[16] The *Bcl*I SNP, located in intron 2 of the *NR3C1*, and the N363S SNPs have been associated with enhanced corticosteroid sensitivity in the general population. On the contrary, the ER22/23EK SNP, located in exon 2 of the *NR3C1*, is associated with relative corticosteroid resistance.[29]

The increase in GRα-A isoform expression induced by the ER22/23EK (rs6189 and rs6190) polymorphism that affects the GCRα-A/GCRα-B ratio and appears in 2% of the general population, is a possible mechanism explaining corticosteroid resistance because it causes a significant reduction of transactivating capacity of GRα.[30]

On the other side, higher methylprednisolone potency at least in vitro is associated with rs41423247, the intronic *Bcl*I polymorphism in the *NR3C1* gene.[31] In effect, it was documented that children with moderate-to-severe asthma exacerbation, who were homozygous carriers of the G allele of rs41423247, showed a higher improvement in FEV_1 at 4 hours when treated with high-dose ICS.[22] However, it has also been reported that corticosteroid resistance can be associated with BclI polymorphism.[32]

The N363S polymorphism (rs6195), located within exon 2 and found in about 4% of the general population, is another genetic variation associated with an increase in corticosteroid sensitivity,[33] although a study was unable to detect major differences between wild-type GR and the N363S polymorphism.[34]

Also the *TthIII*I polymorphism (rs10052957), which is located in the area of the *NR3C1* gene promoter, is associated with corticosteroid resistance. However, it is not functional by itself, but is linked to the ER22/23EK and the observed resistance to corticosteroid likely depends on the ER22/23EK polymorphism.[26,35]

Several studies have investigated the possible association of GR SNP with corticosteroid response in asthmatic patients, in addition to the two studies we have just mentioned. A Polish study showed that, contrary to what could be expected, N363S SNP, but not the ER22/23EK polymorphism, might have an important part in the development of difficult-to-treat/treatment-resistant asthma.[36] Another study documented the absence of any association between GR polymorphisms (*TthIII*I, ER22/23EK, N363S, *Bcl*I) and the dose of ICS needed to achieve asthma control in a group of pediatric patients with asthma.[37] Another two studies, one association study and one mutational analysis, concluded that *NR3C1* does not contribute significantly to corticosteroid resistance.[38,39]

Interestingly, the frequencies of the ER22/23EK, *TthIII*I, and *Bcl*I polymorphisms of the *NR3C1* gene were not statistically different when a comparison was made

between a control group and an asthmatic group, regardless of the severity of asthma.[26]

Another GR SNP, the A829G polymorphism (rs2278008) in exon 5, raises the transactivation potential of GR more than eight times, but the exact mechanism for this hyperactivity is unclear.[40]

The Chaperone Protein Gene Polymorphisms

The stress induced phosphoprotein 1 (STIP1) is a protein that modulates the chaperone activity of HSP70 and HSP90. A number of intronic SNPs in the *STIP1* gene, which is located on chromosome 11q13.1 and is composed of 14 exons, can influence lung function responses to corticosteroids after 4 (rs6591838 and rs223647) and 8 (rs6591838 and rs1011219) weeks of therapy, with the biggest change observed with rs6591838.[41] Mechanisms that contribute to variation in corticosteroid response are still unknown, but interactions with HSP chaperones that influence GR function are a possibility. However, steroid-sensitive patients present a significantly lower ratio of nuclear HSP90/GR than steroid-resistant subjects,[42] and no positive data exist on the association of *HSP90* gene polymorphism and corticosteroid treatment.[16]

The *FKBP4* gene, which maps on chromosome 12, at 12p13.33 and encodes for the immunophilin FKBP52, is thought to be involved in the regulation of GR signaling. It was found that the rs4713916 SNP in the *FKBP4* gene correlated with corticosteroid resistance at least in Crohn's disease.[43]

Usually, the clinical use of ICS in asthma does not take into account all these genetic variants. However, the intrinsic variability in the pharmacokinetics of the prescribed ICS and the effect of the disease itself affect the therapeutic dosage much more than the small differences in corticosteroid sensitivity induced by SNPs.[44]

Other Genetic Alterations in Corticosteroid Pathway

Phosphorylation of GRα at Ser^{226} reduces GR nuclear translocation and induces corticosteroid resistance.[45] The involvement of serine/threonine protein phosphatase 2A regulating c-Jun N-terminal kinase (JNK) 1 and GR-Ser^{226} signaling appears to be a possible mechanism explaining this resistance.

Protein kinase dual-specificity phosphatases (DUSPs) dephosphorylate JNK, and influence the corticosteroid sensitivity.[46] *DUSP1*, which is located on chromosome 5q35.1 and consists of four exons separated by three relatively small introns, encodes a protein that inactivates p38 mitogen-activated protein kinase (MAPK), thereby reducing the expression and production of proinflammatory cytokines.[47] In *DUSP1* knock out mice, dexamethasone is less effective in reducing the release of TNF-α and IL-6 in response to endotoxin injection.[48] The *DUSP1* polymorphisms rs881152, a 5′ region SNP, and rs34507926, located in intron 1, were associated with greater bronchodilator responses and better asthma control in a cohort of asthma patients under a regular treatment with an ICS.[49] The mechanism that explains these effects has not yet been clarified. It is possible that the ability of *DUSP1* to address the p38 MAPK signaling pathway may be changed in carriers of the rs881152 SNP due to a corticosteroid-induced reduction of the *DUSP1* expression.[50]

Histone deacetylase (HDAC) is critical in regulating inflammatory genes because it removes acetyl groups from histones.[51] Increased airway inflammation and larger type 2 cytokine production were observed after deletion of *HDAC1* in T-cells in an in vivo mouse model of allergic airway disease.[52] Corticosteroids perform their anti-inflammatory effects by inducing acetylation of anti-inflammatory genes, but particularly by recruiting HDAC2 to activated inflammatory genes. Acetylated GRs are deacetylated by HDAC2 and subsequently they can suppress activated inflammatory genes.[53] The rs1741981 polymorphism in the *HDAC1* gene located on chromosome 1p35.2-p35.1 and containing 14 exons is significantly associated with a smaller improvement in FEV_1 in response to corticosteroid therapy in asthmatics.[54] However, the rs58677352 polymorphism in the *HDAC2* gene, which maps to chromosome 6q21 and is composed of 14 exons, does not show any relationship with possible changes in pulmonary function induced by corticosteroids.[54]

Genetic Variation in the Pharmacokinetics of Corticosteroids

The safety and efficacy profile of any ICS is influenced by its pharmacokinetic properties, and genetic polymorphisms can modify not only its pharmacodynamic profile, but also the pharmacokinetic behavior producing variability in response to ICSs.[55]

Corticosteroid metabolism occurs primarily in the liver. Generally, ICSs are metabolized to inactive metabolites

through enzymatic transformations. They are substrates for CYP3A4, which is also present in the intestine and lung.[56]

The presence of the rs35599367 (*CYP3A4*22*) allele in patients receiving fluticasone propionate induced a significant improvement in asthma control scores.[57] In another study, the rs776746 (*CYP3A5*3*) SNP was related to asthma control scores in subjects under inhaled beclomethasone treatment.[58] *CYP3A4**22 and *CYP3A5*3*, which are members of the *CYP3A* family of genes located on chromosome 7, abolish the CYP3A4 and CYP3A5 expression and activity, respectively, and thereby extend the presence of the active ICS in the airways, thus prolonging its anti-inflammatory effects.

Also the association between 11β-hydroxysteroid dehydrogenase and glutathione S-transferases enzyme family gene variation and corticosteroid treatment has been reported but all the available information is focused on patients suffering from acute lymphoblastic leukemia.[16]

Although not strictly connected with the classical parameters of pharmacokinetics, there are two aspects of the movement and intracellular distribution of corticosteroids that have prompted pharmacogenetic considerations.

Gene mutations in corticosteroid transporters should be more important for asthmatic patients. P-glycoprotein 170 (P-gp) pumps corticosteroids out of cells and, therefore, it might also be involved in corticosteroid activity/resistance.[59] When its expression is increased, the intracellular drug concentrations decrease and, consequently, also the response to ICSs may decrease The multidrug-resistance gene *MDR1* (*ABCB1*) that maps on chromosomal region 7q21 encodes P-gp.[16,59] Three common *MDR1* SNPs, C1236T (rs1128503), G2677T/A (rs2032582), and C3435T (rs1045642) located on the coding region have an impact in corticosteroid treatment. The rs1128503 polymorphism is associated with an increased risk of steroid resistance at least in children with idiopathic nephrotic syndrome.[60]

Long-term exposure to ICSs may increase P-gp expression and thus reduce the effectiveness of other known P-gp substrate medications, including systemic corticosteroids, when they are administered using standard doses. This could be a issue when a systemic corticosteroid is needed to treat severe asthma.[61] However, it is generally believed that the increased expression of P-gp is not an important mechanism of induction of corticosteroid resistance in asthma[16] and, therefore, it would not compromise the ICS effectiveness.[61]

GR is shuttling between the cytoplasm and the nucleus and its subcellular localization depends on the rate of nuclear import and export. Nuclear import of GR is mediated through its nuclear localization signals (NLSs) and interaction with importins (IPOs) or karyopherins, with IPOα selectively binding to NLS1 and IPO7 and 8 binding to both NLS1 and NLS2.[23] IPOs are known to direct the ligand-activated GR to gated channels of the nuclear membrane, the nuclear pore complex, and cause the translocation of the GR to the nucleus.[62] Small interfering RNAs that inhibited IPO13 synthesis, which also shows export activity,[63] inhibit nuclear translocation of GR.[55] Silencing of *IPO13*, which is a corticosteroid-inducible gene located on chromosome 1p34.1, also abolishes the inhibitory effect of cortisol on TNF-α stimulation of the inflammatory cytokine IL-8 expression.[64] These findings suggest that the anti-inflammatory effects of corticosteroids or, conversely, the induction of corticosteroid resistance, are influenced by variation in cellular levels of IPO13 and intracellular IPO13 shuttling rates. There is documentation that genetic variation of *IPO13* is associated with reduction in airway responsiveness in children with mild-to-moderate asthma not treated with long-term ICSs.[65] Since this improvement was similar to the improvements noted among patients on long-term ICSs, it was suggested that that *IPO13* variation could increase endogenous corticosteroid bioavailability in the cell nucleus. It is obvious to wonder whether the presence of such a variation could lead us to avoid the use of ICSs or to recommend their use at lower doses. Regrettably, no other studies have been conducted on this topic, so the question is still unanswered.

Other Genetic Variations That Can Modify the Corticosteroid Activity

Many other SNPs that are even outside the corticosteroid pathway, but have the potential to influence the corticosteroid activity have been described.

Thus, the presence of a deletion polymorphism (rs3842689) of the pregnane X receptor gene (nuclear receptor subfamily 1, group I, member 2, *NR1I2*), which is located on chromosome 13q12-q13.3, has been associated with unresponsiveness to corticosteroids. In effect, a reduced expression of pregnane X receptor leads to an underexpression of GRs.[66]

Improvement in bronchial hyperresponsiveness or better bronchoprotection during ICS treatment have been associated with another SNP, rs2240017, which is encoded by the T-box expressed in T-cell transcription that

regulates naïve T-lymphocyte development (*TBX21*) gene which maps on chromosome 17q21.32.[67]

However, in these last years genome-wide association studies (GWASs), which allow analyzing hundreds of thousands of SNPs with the aim of associating them to a better or worse drug response, have been performed.

A GWAS revealed that there is a significant association between the genetic polymorphism rs37972 in the promoter region of the glucocorticoids-induced transcript 1 (*GLCCI1*) gene, which is located on chromosome 7p21.3 and encodes a protein of unknown function, and a decreased response to ICS therapy in asthmatic patients.[68] This SNP is in complete linkage disequilibrium in the same gene with the rs37973 SNP, which can influence *GLCCI1* gene expression. However, another study did not confirm that *GLCCI1* rs37973 is able to predict the response to ICSs.[69] Little is known about the real function of *GLCCI1* in humans. It was originally described as a thymocyte-specific transcript that is quickly upregulated in response to dexamethasone treatment.[70] *GLCCI1* deficiency in asthmatic mice does not allow the activation of GR and mitogen-activated protein kinase phosphatase 1. Furthermore, it causes an increased phosphorylation of p38 MAPK, leading to a decremented response to corticosteroids.[71]

The intronic rs10044254 polymorphism has been identified in two independent pediatric cohorts (average age 8.9 and 10.4 years, respectively), but failed to be replicated in an adult asthmatic population (33–34 years old on average).[72] It is associated with both decreased expression of the F-Box and Leucine Rich Repeat Protein 7 (*FBXL7*) gene, which maps on chromosome 5p15.1, and improved symptomatic response to ICSs. This finding suggests that there might be a specific genetic mechanism able to regulate symptomatic response to ICSs only in children. However, recently *FBXL7* has been identified as a male specific gene in epithelial cells of asthmatic subjects although, unfortunately, it was not specified whether they were adults or children.[73]

Two variants of the orosomucoid like-3 (ORM1-like protein 3; *ORMDL3*) gene, which is located in chromosome 17q21 and encodes for a protein that is an important mediator in diminishing the synthesis of sphingolipids, rs2872507, that is intergenic,[74] and rs72821893, which was located in the same chromosomal area,[75] are associated with ICSs treatment response in atopic subjects. Sphingolipids have a central role in synthesizing many inflammatory proteins.[76]

The polymorphism rs2146323 of the vascular endothelial growth factor A (*VEGFA*) gene, mapped to chromosome 6p12, was associated with response to ICS therapy in asthma patients.[77] In an animal model, VEGF A increases mucus production, collagen deposition, as well as smooth muscle hyperplasia.[78] However, the functional implications of rs2146323 are uncertain because this SNP is located in a non-coding exon area.[79]

Another GWAS found a significant association between the SNP rs2392165 near the Bardet-Biedl syndrome 9 (*BBS9*) gene mapped on chromosome 7p14.3 and ICS use when treating wheezing/coughing, with better ICS response.[80] *BBS9* is implicated in lung development and ciliogenesis.

The Fc fragment of IgE receptor II (*FCER2*) gene, which is an 11-exon gene located at chromosome 19p13.2 and encodes for a low affinity IgE receptor, offers the most consistent results in candidate gene studies. The rs28364072 (T2206C) polymorphism in *FCER2* gene located 7bp 3′ of exon 9 can predict low-response to ICS in childhood asthma.[81,82] Mutations in the *FCER2* gene might alter the ability of a subject to downregulate the IgE pathway that is inherently relatively resistant to corticosteroid-induced downregulation, with resulting poorer long-term outcomes in both lung function and exacerbations.[2]

However, other GWASs on ICS response in asthmatic population did not find any significant finding.[83] A fundamental GWAS on the pharmacogenetics of ICS response in 2672 patients with asthma investigated more than 9.8 million genetic variants (minor allele frequency ≥1%).[84] Common genetic variants or rare genetic variants with large effect sizes did not influence the variability in ICS treatment response in these patients and did not predict an individual's response.

Differences in ICS Response by Genetic Ancestry

There is often a link between the frequency of a SNP and race/ethnicity.[85] Actually, SNPs cluster within groups and are more likely to share a common region of origin or ancestral lineage. Data from the NHLBI Severe Asthma Research Program suggest that several genetic polymorphisms, such as rs17142727 in *GLCCI1* and rs1429032 and rs6867762 in *FBXL7* in non-Hispanic Whites, and rs1476823 in *GLCCI1*, rs7801671 and rs7801671 in *CYP3A4*, rs4701641 and rs12152734 in *FBXL7*, and rs17689966 in *CRHR1* in African-Americans could be associated with changed ICS

responsiveness.[85] Apparently, the polymorphism rs37972 of *GLCCI1* gene rs37972 is less common in populations of African descent compared with a European population.[68] A GWAS in asthmatic Hispanic/Latino and African-American children and young adults was unable to find any consistent association with ICS response of 22 SNPs previously associated with this response in another GWAS.[86] However, it discovered that the A allele of rs5995653, located 5.8 kb from the 3′UTR of the apolipoprotein B mRNA-editing catalytic polypeptide 3 (*APOBEC3*) gene, was associated with improvement in FEV_1 in patients treated with ICS.

In any case, the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE) documented that the self-declared race ethnicity and genetic ancestry do not predict ICS response, in contrast to the baseline measures of lung function and self-reported asthma control.[87] This finding strongly supports the opinion that ICSs are useful in treating asthma, regardless of racial background.[87]

Conclusion

Theoretically, responses to ICS in asthma are influenced by different genetic variants. However, the replication of pharmacogenetic findings is scarce and we are still far from using them in our clinical asthma practice. This is arguably explained by the fact that response to corticosteroids is too complex to be mainly conditioned by a few genetic variants.[13] Nevertheless, it is a real limitation because in an era of precision medicine that links the right patient to the right treatment,[88] knowing and dealing with the genetic factors that influence the therapeutic ICS response is fundamental for making precision medicine socially and scientifically accurate.

Although there has been considerable progress, currently known genetic loci only account for a fraction of variability in drug response. In fact, too many different proteins are involved in the response to asthma drugs,[89] in particular ICSs. We strongly believe that in examining the role of single SNPs, the epigenetic changes must always be considered because they can modify genetic effects in time-, environment-, and tissue-specific manners.[13] ICS use has been shown to affect epigenetic patterns. Active and passive smoking is a typical example because it impairs HDAC2 activity, which could contribute to corticosteroid-insensitive inflammation in patients with severe asthma.[90] Furthermore, since genes interact epistatically (ie, together) in networks, this gene-gene interaction must always be considered being critical for expanding the amount of phenotypic varieties that can be attributed to genetics.[91]

In order to overcome this big issue the possibility of integrating multiple omics layers seems an interesting new approach.[92] Connecting genetics with two or more layers will likely maximize the information obtained from different layers. It will allow better understanding of the underlying biological pathways of the multifactorial disease process of asthma. If we will be able to analyze and integrate this information, we likely will generate a systems medicine view of the molecular processes underlying the development and progression of asthma. This will allow us to prescribe the right dose of ICS to the right patient at the right time.

Author Contributions

All authors made substantial contributions to conception of the article; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

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