Glucocorticoids in Pediatric Gastrointestinal Disorders

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Pediatric Inflammatory Bowel Disease

Inflammatory bowel diseases (IBDs) are the most frequent chronic gastrointestinal disorders in pediatric age. They include two disease entities – Crohn's disease (CD) and ulcerative colitis (UC) – which, although different in their pathogenesis, show common clinical characteristics such as chronic inflammation at different levels of the gastrointestinal tract and alternation between active and inactive phases. The incidence of IBD is increasing in recent years, particularly among children and adolescents, and it is currently estimated that 20–30 % of patients with IBD experience the onset of symptoms when they are under 20 years of age [1–3]. In childhood, IBDs are generally more extended, more severe, and progress more rapidly than in adulthood. Moreover, therapy in children with IBD is more aggressive than in adults: Indeed, about 80 % of children need steroids, and about 30 % are subjected to an intestinal resection during a 5-year follow-up. Quality of life is severely affected in IBD, especially for pediatric patients, owing to the chronic character of the disease that implies frequent hospitalizations and aggressive therapies, with a significant risk of side effects and a considerable impact on health care costs. IBD can result in loss of education and difficulty in gaining employment or insurance; overall, 15 % of patients with IBD are unable to work after 5–10 years of disease. Depressive disorders and low social functioning are also common among these patients, and the disease can also cause growth failure or retarded sexual development in young people [4–7]. It was recently reported that the mean individual annual costs in European countries amount to US$6,000 for CD and $4,600 for UC, and pediatric cases cost even more than adult ones [8].

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Induction of Remission with Glucocorticoids

UC and CD are complex disorders characterized by a wide variation in clinical characteristics. To date, treatment goals in IBD are evolving beyond the control of symptoms toward the tight control of objectively measured gastrointestinal inflammation [9]. Glucocorticoids (GCs) have been used to treat patients with active IBD for nearly 50 years [10], and despite the introduction of highly effective biological drugs in therapy, in patients with moderate to severe IBD GCs are still used to induce remission. In UC with pancolic localization, GCs are the gold standard for treatment and are always the first choice. In CD with pediatric onset, the first-line therapy is exclusive enteral nutrition: It is generally used for induction of remission and is achieved within 6–8 weeks of exclusive liquid feeding with either elemental or polymeric formulae [11]. In children with moderate to severe active luminal CD, oral corticosteroids are recommended for inducing remission if exclusive enteral nutrition is not an option.

In addition, in cases of CD with colic localization and with extraintestinal manifestations or severe prognosis (perianal disease, extensive disease), today the trend is to use immediately anti-tumor necrosis factor-α biologic agents, in an attempt to change the natural history of the disease.

When GCs are needed, oral prednisone is the agent of choice, and the standard treatment consists in administration of prednisone 1–2 mg/kg/day for 2–3 weeks (maximum dose 50 mg/day) and subsequent dose tapering every week. Different clinical responses have been observed with these agents in IBD; indeed, up to 90 % of pediatric patients have a rapid improvement of symptoms when a prednisone equivalent of 1–2 mg/kg/day is given [12]. After 1 year, only 55 % of early steroid-treated patients are still in remission and are deemed steroid-responsive, while around 38 % of patients are not able to discontinue the therapy and experience an increase in disease activity when the dose is reduced or during the first year after discontinuation; these patients are considered steroid-dependent. Seven percent of subjects are resistant and do not respond to GC therapy [13, 14]. In adults, steroid-dependence is more restrictive than in children, and is defined as the inability to taper GCs to less than 10 mg/day within 3 months of starting steroids without recurrent disease, or as the occurrence of relapse within 3 months of stopping GCs.

In children with mild to moderate ileocecal CD, budesonide may be used as an alternative to systemic corticosteroids for induction of remission [15]. The drug is taken orally and released in the distal small bowel and proximal colon; acting locally, this agent causes fewer systemic side effects. In subjects with mild to moderate ileal–right colonic disease, 9 mg of budesonide daily was superior to 4 g/day of mesalamine in inducing remission at 8 weeks (69 % vs. 45 %) and 16 weeks (62 % vs. 36 %) [16, 17].

Side Effects Associated with Glucocorticoid Treatment

The risks for adverse effects of GCs are related to the dose and the length of treatment, but sensitivity among individuals may vary greatly [15].

Growth failure and delayed puberty are present in a great proportion of children with IBD as a consequence of the disease and require particular attention; these conditions may be primarily related to malnutrition and to the strong inflammatory reaction occurring during active disease [18, 19, 20]. Furthermore, GC therapy, although efficient in inducing remission, clearly shows deleterious effects on growth. The mechanisms by which GCs suppress growth are complex. Pediatric patients with active IBD already have abnormal bone turnover [21], but GC exposure leads to promotion of osteoblast and osteocyte apoptosis, resulting in reduced bone formation, and these effects end with GC withdrawal [22, 23]. In addition, emerging evidence suggests these conditions could increase the risk of vertebral fractures in pediatric patients with IBD treated with GCs [24], but the minimum dose and duration of therapy that may cause damage to bones and fractures in children with IBD are currently unknown. Conversely, the negative effects of GCs on bone may be offset by their capacity to reduce inflammation.

Another important side effect observed in pediatric patients with IBD treated with GCs is adrenal suppression. This is a condition in which adrenal glands do not produce adequate amounts of cortisol when GC therapy is stopped, and is caused by suppression of the hypothalamic–pituitary–adrenal (HPA) axis by the circulating exogenous GCs [25, 26]. Sidoroff and colleagues [25] showed that at least one fifth of pediatric patients with IBD present with abnormal or even undetectable serum cortisol values at the end of systemic GC treatment. For patients with low levels of cortisol, hydrocortisone substitution was introduced until observing cortisol values within normal range.

Other common side effects include acne, facial hair growth, weight gain, and rounding of the face, and most of these will decrease when the drug is tapered down and discontinued. These side effects can trouble the patient, particularly female patients and/or adolescents, and can influence negatively compliance to therapy, especially in the case of repeated cycles of treatment.

Glucocorticoid Resistance in IBD

In inflammatory diseases, GC resistance or dependence is particularly frequent. As reported in the previous section, clinical studies in pediatric patients with IBD have shown that up to 90–95 % of subjects had a rapid improvement of symptoms when prednisone is given, but 5–10 % of patients still showed active disease [12, 27]. In addition, around 40 % of patients are considered dependent: They are not able to discontinue the therapy and experience an increase in disease activity when the dose is reduced or they relapse within 1 year of treatment suspension.

The phenomenon of GC resistance in chronic inflammatory diseases should be separated from the rare familial condition of primary generalized GC resistance, for which the name Chrousos syndrome was recently proposed [28]: This is a rare, sporadic, or familiar syndrome caused by mutations in the *NR3C1* (nuclear receptor subfamily 3, group C, member 1) gene. The disease is characterized by target tissue

insensitivity to GCs due to reduction or lack of functional GC receptors and by compensatory elevation in adrenocorticotropic hormone (ACTH). This results in an increased secretion of cortisol, albeit in the absence of signs of Cushing's syndrome, as well as of other adrenal hormones with mineralocorticoid and androgenic activities, which is responsible for the main symptoms (hypertension and signs of hyperandrogenism). As mentioned, however, this syndrome is extremely rare, and no cases in patients with IBD have been described in the literature [29].

The most common forms of resistance observed in chronic inflammatory conditions, and in IBD in particular, may occur at several levels in the complex GC mechanism of action.

Molecular Mechanism of GC Action

The effects of GCs are mediated by the glucocorticoid receptor (GR)-α, a member of the nuclear receptor superfamily of ligand-dependent transcription factors [30, 31]. The human GR gene (*NR3C1*) is located on chromosome 5q31.3 and consists of nine coding exons [32]. Alternative splicing of exon 9 generates two receptor isoforms, GR-α and GR-β [33–36]. GR-β is not able to bind GCs, resides constitutively in the nucleus of cells, has a longer half-life than GR-α, and does not transactivate GC-inducible reporter genes [37]. It has been suggested [38, 39] that cell-specific expression and function of GR isoforms may explain the tissue- and individual-selective actions of GCs.

The function of GR is conditioned by chaperone and cochaperone proteins that form a molecular heterocomplex with the GR itself [40, 41], required for proper ligand binding, receptor activation, and transcription: Abnormalities in proteins that make up the heterocomplex may contribute to altered GC responsiveness [42, 43]. Several studies have demonstrated differences in the heterocomplex gene expression profiles in steroid-resistant versus steroid-responsive patients, but it is not clear if this different expression is the cause of the variability in response or the consequence of GC treatment [28, 44–48]. After GC binding and dissociation from heterocomplex proteins, the GR translocates into the nucleus; translocation is mediated by specific nuclear transport factors that belong to the importin-β family of nuclear transporters, and in particular by importin 13 [49]. The activated receptor then binds as homodimer to two palindromic DNA-binding sites, the so-called GC-responsive elements (GREs), localized in the promoter region of target genes [50–52]. As a consequence of DNA binding, GCs can induce transactivation and transrepression processes: Binding to positive GREs leads to activation of the transcription of anti-inflammatory [e.g., interleukin-10 (IL-10), annexin 1] as well as of regulator proteins involved in metabolic processes (e.g., enzymes of gluconeogenesis) [53–55].

The second mechanism of GC action is transrepression [56], which leads to a reduced expression of immune-regulatory and proinflammatory proteins such as cytokines (IL-1, IL-2, IL-6, tumor necrosis factor-α) and prostaglandins [57], and is

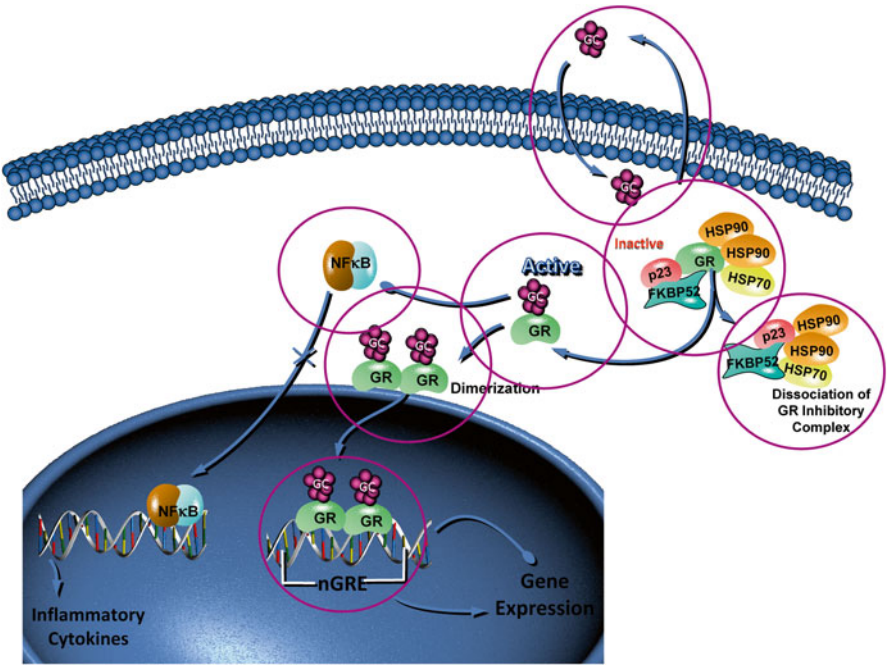

Fig. 1 Molecular mechanism of glucocorticoid action. *GR* glucocorticoid receptor, *GC* glucocorticoid, *HSP* heat-shock protein, *FKBP* FK506-binding protein, *NF-kB* nuclear factor-kB

believed to be responsible for the majority of beneficial anti-inflammatory effects. Furthermore, GRE-independent mechanisms of transrepression also exist: The GR physically interacts with activator protein-1 [58], nuclear factor-kB [59], and signal transducers and activators of transcription [60].

Steroid hormones can also regulate gene expression posttranscriptionally, by destabilizing mRNAs [61]. In addition, these hormones can induce rapid nongenomic effects within the cytoplasm; for example, they induce the release of Src kinase from the GR heterocomplex, resulting in lipocortin activation and inhibition of arachidonic acid release [62, 63], and they alter cytoplasmic ion content [64, 65] (Fig. 1).

Genetic and Epigenetic Predictors of GC Response

Given the high incidence of suboptimal response, associated with a significant number of side effects, the identification of subjects who are most likely to respond poorly to these agents seems extremely important. However, the mechanisms of steroid resistance and/or dependence are scarcely understood and there is presently no means to predict the response in advance.

Demographic and/or clinical markers [10, 66, 67] have been examined in correlation with GC response, but results have not been consistently replicated and could not be translated into clinical practice. Genetic markers are likely to complement clinical and demographic predictors. Phenotypes resulting from genetic changes, such as single nucleotide polymorphisms (SNPs), deletions, insertions, and duplications in genes involved in the complex GC mechanism of action can markedly influence drug pharmacokinetics or alter efficacy and/or toxicity profiles; in particular, genetic variants in the GR receptor heterocomplex, in the proinflammatory mediators in the downstream signaling pathway of the GC–GR complex, and in proteins involved in the extrusion (P-glycoprotein) and metabolism of GCs have been evaluated in the literature.

In addition, new genetic biomarkers have been studied: microRNAs (miRNAs), small noncoding RNA molecules that suppress the expression of genes involved in drug molecular mechanisms, have emerged as a promising field of pharmacogenomic research. Here we focus our attention on GR, which has a central role in GC molecular mechanisms, considering polymorphisms in its gene and the expression of miRNAs involved in its regulation.

GR Gene Polymorphisms

The human GR gene, *NR3C1* (nuclear receptor subfamily 3, group C, member 1; Nuclear Receptor Nomenclature Committee, 1999), is located on chromosome 5q31.3 and includes nine exons [32]. Polymorphisms of this gene may impair the formation of the GC–GR complex and subsequently alter transactivation and/or transrepression processes that have been related to increased [68] or decreased [69] sensitivity to endogenous cortisol.

The *TthIII*I (rs10052957), ER22/23EK (rs6189/rs6190), GR-9β (rs6198), N363S (rs6195), and *Bcl*I (rs41423247) polymorphisms have been the most studied and have been associated with differences in metabolic parameters and body composition as well as with autoimmune and cardiovascular disease. These genetic variants have also been related to changes in GC sensitivity [70] and may therefore account for the variability in the response to GC therapy. Although very few studies deal with the mechanisms, it is usually assumed that NR3C1 polymorphisms lead to a modified GR transcript.

*TthIII*I (rs10052957) is a restriction fragment length polymorphism (RFLP) caused by a C>T change in the GR gene promoter region; it is located in a large intron of approximately 27 kb, 3,807 bp upstream of the GR start site [71]. This polymorphism has been associated with elevated diurnal cortisol levels and with a reduced cortisol response to 1 mg dexamethasone (DEX), as well as lower insulin and cholesterol levels [68]. Other studies suggest that this polymorphism has a biological role mainly in association with other GR polymorphisms, forming haplotypes [72], but to date it has not been correlated with clinical response to GCs in patients with IBD, neither alone nor in haplotype.

The ER22/23EK polymorphisms (rs6189+rs6190) are located in the N-terminal transactivation domain of the GR and involve two nucleotide changes in codons 22 and 23 of exon 2 (GAG AGG to GAA AAG), which change the amino acid sequence from glutamic acid–arginine (E-R) to glutamic acid–lysine (E-K). Since the polymorphism is located in the transactivation domain, the amino acid change might affect the receptor's tertiary structure, influencing the transactivational and/or transrepressional activity on target genes [73]. An association with higher post-DEX cortisol levels and less cortisol suppression after a 1 mg DEX suppression test in ER22/23EK carriers has been shown. In addition, the polymorphism is associated with a better metabolic and cardiovascular health profile and an increased survival [68, 69]. In a study considering the role of ER22/23EK in the variability of clinical response to GCs in IBD, no association was found between the ER22/23EK polymorphism and GC response in 119 pediatric patients [74]. These polymorphisms have been also studied in adult patients with IBD, but no correlation has been observed with GC-resistant phenotype, even when dividing patients into UC and CD groups [75].

GR-9β (rs6198) is an A to G nucleotide substitution located in the 3'-UTR of exon 9β, the terminal exon of the mRNA of the β isoform (nucleotide 3669 in X03348; rs 6198). The A to G nucleotide substitution is located in an ATTTA motif (changing it to GTTTA). This ATTTA motif is known to destabilize mRNA and decrease receptor protein expression *in vitro* [76, 77]. GR-β, generated through an alternative splicing [78], is unable to bind ligand, is transcriptionally inactive, and exerts a dominant negative effect on transactivation by interfering with the binding of GR-α to the DNA [79, 80]. Honda et al. [81] reported GR-β specific mRNA expression in lymphocytes of 83 % of patients with steroid-resistant UC compared with only 9 % in responsive subjects and 10 % in healthy controls and patients with chronic active CD. This observation was confirmed in colonic biopsies of patients with UC: Significantly more GR-β-positive cells were seen in the resistant group than in the GC-sensitive and control group [82]. However, in IBD, GR-β is expressed 100–1,000 times less than GR-α, and this challenges its role in the genesis of steroid resistance in this disease. The role of *TthIII*I, ER22/23EK, and GR-9β has been investigated in association with the response to exogenous GCs. The combinations of the three polymorphisms were studied in 646 patients with multiple sclerosis treated with GCs. In this study, the haplotype consisting of *TthIII*I, ER22/23EK, and 9β-G was associated with GC resistance and with a more rapid disease progression. However, this seemed to result from the presence of ER22/23EK and not from the other two polymorphisms [83].

Two single nucleotide polymorphisms in the *NR3C1* gene, the N363S and *Bcl*I polymorphisms, have been, on the other hand, associated with an increased sensitivity to GCs. The N363S polymorphism, originally rs6195, currently listed in dbSNP as rs56149945, results in an asparagine (N) to serine (S) change in amino acid in codon 363. The N363S polymorphism may influence the interaction of the GR with coactivators and/or corepressors, one of the known functions of the N-terminal domain of this receptor [76]. Only few reports have studied the role of this polymorphism in the response to exogenous GCs. In 102 patients who underwent photore-

fractive keratectomy and received topical steroids as part of postoperative therapy, a significant correlation was found between N363S heterozygosity and ocular hypertension [84]. Furthermore, in 48 patients with Duchenne muscular dystrophy treated with prednisolone or deflazacort, the N363S carriers showed a trend toward a later age at loss of ambulation in comparison with noncarrier patients [85]. Only two studies to date have evaluated the role of this polymorphism in GC clinical response in IBD, but no relation was observed between the presence of this SNP and response to GCs both in pediatric and in adult patients [74, 75].

The *Bcl*I polymorphism (rs41423247) was initially described as a polymorphic restriction site inside intron 2, the nucleotide alteration was subsequently identified as a C > G substitution, 646 nucleotides downstream from exon 2 [86]. The molecular mechanism through which the *Bcl*I polymorphism exerts its effect is unknown. This polymorphism is associated with a clinical phenotype consistent with increased GC sensitivity in both heterozygous and homozygous carriers of the G allele. An association with unfavorable metabolic characteristics, such as increased body mass index and insulin resistance, has been also described [87]. The *Bcl*I SNP has been studied in 119 pediatric patients with IBD (64 with CD, 55 with UC). Patients were divided into two groups based on their response to GC treatment: GC dependence (45 patients) was defined by an initial response to prednisone with relapse on dose reduction, not allowing for steroid discontinuation, and GC responsiveness (67 patients) was defined as GC withdrawal without the need for steroids for at least 1 year. A significantly higher frequency of the *Bcl*I-mutated genotype was observed in the GC-responsive patients than in the GC-dependent group [74]. These results have been subsequently confirmed in a larger cohort of young patients with IBD [88] (Table 1).

miRNAs Involved in GR Regulation and Their Potential Role

Recently, noncoding miRNAs have emerged as important gene expression regulatory elements; understanding of the complex gene regulation may shed light on the causes of the variable responses to these hormones in patients with GC-sensitive or GC-resistant inflammatory and autoimmune diseases [89].

miRNAs are small (18–24 nucleotides) noncoding RNAs, which bind the 3′UTRs and the coding exons of their target genes and inhibit gene expression [90] either by messenger RNA (mRNA) cleavage (most common in plants) or by translational repression (most common in metazoan) [91, 92]. A single miRNA can regulate approximately 200 mRNAs, and each mRNA can be regulated by multiple miRNAs [93, 94]; overall, it is predicted that protein production for at least 20 % of all human genes is regulated by miRNAs [95, 96]. miRNAs suppress gene expression at the posttranscriptional level, and are fine-tuning regulators of diverse biological processes, including the development and function of the immune system, apoptosis, metabolism, and inflammation. Emerging data have implicated the deregulated expression of certain miRNA networks in the pathogenesis of

Table 1 Polymorphisms in the glucocorticoid receptor (GR) gene associated with altered glucocorticoid (GC) response in patients with inflammatory bowel disease (IBD) and other diseases

GR gene polymorphisms	Correlations with GC response in IBD or other diseases	References
TthIIIΙ (rs10052957)	Correlation with elevated diurnal cortisol levels and reduced cortisol response to 1 mg dexamethasone (DEX), as well as lower insulin and cholesterol levels	[68]
	No correlation in haplotype with clinical response to GC in IBD patients	[72]
ER22/23EK (rs6189/ rs6190)	Association with higher post-DEX cortisol levels and less cortisol suppression after a 1 mg DEX suppression test	[69]
	Correlation with a better metabolic and cardiovascular health profile and an increased survival	[70]
	In 119 pediatric patients with IBD, no association with GC response	[74]
	In adult IBD patients, no correlation with GC-resistant phenotype even when dividing patients into UC and CD	[75]
GR-9β (rs6198)	Association of the haplotype consisting of *TthIIIΙ*, ER22/23EK, and GR-9β-G with GC resistance, and with a more rapid disease progression	[83]
N363S (rs6195)	Significant correlation with ocular hypertension in 102 patients who underwent photorefractive keratectomy and received topical steroids	[84]
	In 48 patients with Duchenne muscular dystrophy treated with prednisolone or deflazacort, correlation with a later age at loss of ambulation	[85]
	No correlation with response to GCs in pediatric IBD patients	[74]
	No correlation with response to GCs in adult IBD patients	[75]
BclI (rs41423247)	In 119 pediatric patients with IBD, association with GC response	[74]
	Unfavorable metabolic characteristics, such as increased body mass index and insulin resistance	[87]

autoimmune and inflammatory diseases, such as IBD, and it has been suggested that these small noncoding RNAs represent an important player in the complex interactions that result in IBD clinical features [97–100]. A number of studies have identified a specific differential expression of miRNAs in IBD and unique miRNA expression profiles for the different subtypes of IBDs and for evolutionary stages of the disease in colonoscopic biopsies [97, 101]. In particular, Zahm and colleagues [102] identified a number of miRNAs significantly increased in the serum of patients with pediatric CD in comparison with healthy subjects. In addition, Wu and colleagues demonstrated for the first time that peripheral blood miRNAs can distinguish active IBD subtypes from each other and healthy controls. They identified 10 miRNAs significantly increased and 1 miRNA significantly decreased in

the peripheral blood of patients with active UC as compared with patients with CD, 12 miRNAs significantly increased and 1 miRNA significantly decreased in the blood of patients with active UC compared with healthy controls, and 5 miRNAs significantly increased and 2 miRNAs significantly decreased in the blood of patients with active CD compared with healthy controls [103]. Paraskevi and colleagues recently identified 11 miRNAs significantly increased in CD and 6 miRNAs increased in UC blood samples compared with healthy controls [104]: These results confirmed previous studies of IBD miRNA expression obtained in blood and/or tissue samples [98, 105].

In this context, the study of a possible correlation between tissue or blood miRNA expression and variability in GC response in pediatric patients with IBD could be a promising field of research. The investigation of miRNA expression as a pathogenetic or pharmacological biomarker in plasma, serum, or peripheral mononuclear cells instead of colonic tissues represents a semi-invasive diagnostic approach, easier to translate into clinical practice, particularly in a pediatric population. Indeed, an ideal biomarker must be easily accessible using noninvasive procedures, and this is especially true when the patients are children.

An important field of investigation concerns the role of miRNAs in the regulation of target genes, such as *NR3C1*. Computational studies showed that the 3′ UTR of the GR gene is predicted to contain numerous seed regions recognized by a variety of miRNAs [106].

Vreugdenhil and collaborators investigated the possible interaction between miRNAs and *NR3C1*, and they found that miR-18 and miR-124a bind GR mRNA and decrease GR activity in neuronal tissues, using a combination of *in silico* prediction of miRNA binding sites, miRNA overexpression studies, and mutagenesis of the GR 3′ UTR [107]. The overexpression of these miRNAs reduced GR protein levels and impaired the activation of the GC-responsive gene glucocorticoid-induced leucine zipper (*GILZ*) in neuronal cell cultures. In addition, these authors demonstrated by miRNA reporter assay that miR-124a is able to bind to the predicted seed region in the GR 3′UTR.

The role of miR-124 has been investigated in the regulation of GR expression in human T cells of patients with critical illness-related corticosteroid insufficiency. It was found that miR-124 specifically downregulated GR-α, and a slight increase of miR-124 and a reduction of GR-α were observed in patient T cells compared with healthy controls [108]. In addition, Tessel and colleagues [109] identified and characterized miR-130b as an important downregulator of GR in a GC-resistant multiple myeloma cell line: The overexpression of this miRNA was also associated with a decreased regulation of *GILZ*, a downstream GC-controlled gene (Table 2).

Table 2 Role of miRNA deregulation in inflammatory bowel disease (IBD) considering glucocorticoid receptor (GR) as target

Sample analyzed	Correlations	References
Patient colonoscopic pinch biopsies	miRNA expression changes during tissue inflammation, and patterns of miRNAs are intestine region-specific	[101]
Patient peripheral blood	miRNAs in peripheral blood can distinguish active IBD subtypes from each other and healthy controls	[103]
Patient serum	miRNA profiles significantly increased in the serum of patients with pediatric CD in comparison with healthy subjects	[102]
Patient blood samples	Pattern of 11 miRNAs significantly increased in CD and of 6 miRNAs in UC	[104]
In vitro neuronal cell cultures	miR-18 and miR-124a bind GR mRNA and decrease GR activity	[107]
Patient T cells	miR-124 in patients with critical illness-related corticosteroids insufficiency specifically downregulated GR-α	[108]
GC-resistant multiple myeloma cell line	miR-130b is an important downregulator of GR	[109]

CD Crohn's disease, *UC* ulcerative colitis

Conclusions

GCs have been used in the treatment of active IBD since the 1950s, and are still used to induce remission in pediatric IBD, but interindividual differences in their efficacy and several side effects have been reported. The main goal for clinicians is therefore to improve the efficacy and safety of these agents and, when possible, to reduce steroid exposure and use a nonsteroid option. This is particularly important in patients who do not respond and will suffer considerable steroid-dependent morbidity without any clinical gain. The molecular mechanisms involved in the variability in GC response are still not completely known, but advances in pharmacogenomics could contribute to the optimization and personalization of therapy. Pharmacogenomic studies represent a promising field of research that could increase our understanding of the pharmacology of steroids in IBDs and possibly in other diseases.

In conclusion, the identification of pharmacological, genetic, and epigenetic determinants associated with GC response in pediatric patients with IBD and the consequent personalization of therapy based on this information will result in higher quality, less toxicity, and a more rational employment of national health service resources.

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