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EDITORIAL COMMENTARY

Dosing of glucocorticosteroids in nephrotic syndrome

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Summary

Pharmacodynamic actions and molecular mechanisms of corticosteroids in patients with nephrotic syndrome (NS) are poorly understood. The role of immunosuppressive and of direct stabilizing effects on the podocyte cytoskeleton needs to be defined. Without precise knowledge of the pathogenesis, optimal dosing cannot be established. The finding of Saadeh et al. [1] that dosing of glucocorticoids per body surface area is superior to dosing per kilogram body weight (BW) in terms of reducing the recurrence rate of NS is interesting; however, an overriding effect of age cannot be ruled out.

It is unlikely that all patients with an initial presentation of NS require the same amount of glucocorticoid treatment as patients with recurrent disease. In the future, it may be more important to establish individual treatment strategies than to adapt high doses of glucocorticoids according to anthropometric measurements.

Scope of the problem

A prednisone dose of 60 mg/m^2/day as well as one of 2 mg/kg BW/day are internationally accepted as standard doses in children with NS. In 2009, Feber et al. convincingly demonstrated that prednisone dosing per kilogram body weight or per body surface area are not equivalent for small children [2]. Dosing based on body weight results in an absolute smaller dose than that calculated on the basis of body surface area. In this issue of *Pediatric Nephrology*, Saadeh et al. describe for the first time the effect of weight-based relative 'underdosing' of prednisone [1]: while the initial response was not influenced by such 'underdosing', the frequency of relapses during the first 6 months appeared to be higher in this relatively 'underdosed' group. This result is an argument for a prednisone dosing regimen based on body surface area, at least for the initial and relapse treatment of NS in children. The most important implication of this type of reasoning—if it is indeed correct—is that the relatively higher dose calculated on the basis of body surface area is the optimal dose for achieving the therapeutic effect. The differences in doses would then explain the observed variation in therapeutic results. However, important questions must be answered before this treatment regimen can be approved on the basis of pathophysiology and pharmacology. Therefore, we would like to extend the discussion on dosing to poorly understood fundamental aspects of glucocorticoid actions in NS, which may be fruitful fields for basic and clinical research in pediatric nephrology.

Is 60 mg prednisone/m^2/day the approved optimal treatment dose for the initial manifestation of NS?

In the 1970s, the members of the International Study of Kidney Disease in Children (ISKDC) Study Group agreed on a dose of 60 mg/m^2/day prednisone for 4 weeks followed by 40 mg/m^2/day as the standard treatment for the initial manifestation of NS as the basis for seminal international prospective studies. The agreement was mainly based on personal clinical experience and a review of the literature, but at that time no dose-finding studies had

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been performed. The amount of the steroid dose decided upon was clearly influenced by the intention to successfully treat as many patients as possible as 'steroid sensitive' and to define 'steroid resistance' (non-responders). The genetic basis of steroid-dependent (SD) NS and steroid-resistant (SR) NS was not known at this time.

The dosing proposal of the ISKDC was adopted as the standard dose by other study groups, such as the German Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) to provide a basis for comparison. Between the 1970s and 1990s, the APN performed many important studies using this dose based on body surface area. The results of these studies contributed to the acceptance of the ISKDC dose as optimal for treatment. Likewise, a recent Cochrane analysis has identified 'high doses' and longer treatment duration as effective measures to reduce the frequency of relapses [3]. However, it must be emphasized that the Cochrane meta-analysis is based only on the conservatively high doses used by study groups and the data are far from the answer to the question on the optimal dose.

Also, the general question of whether it is even appropriate to dose corticosteroids according to body mass remains unanswered. It is known, however, that body mass-based dosing is not ideal for determining treatment regimens with other hormones, such as thyroxin, vitamin D, or erythropoietin [4].

Limitations of the Saadeh study

The study by Saadeh et al. [1] is rather limited by the small number of patients, its retrospective approach, and its association design. An example of the pitfalls of too few patients is the painful experience of the APN: due to an insufficient number of patients, the absolute number of relapses in the standard treatment groups varied from one study to the next [5, 6]. In addition, the association of relative 'underdosing' and more frequent relapsing within a short observation period of only 6 months has clearly been biased by the relative high number of drop-outs, as well as age differences between the patients.

The main findings show no difference in primary response, but a difference in the relapse pattern. However, the results, similar to those of a number of earlier studies [7–9], point towards an age effect on the probability of relapses. The prospective studies of Hoyer et al. [7, 9] were the first to highlight this problem: younger age was associated with a significantly higher risk for subsequent relapse, despite the fact that prednisone dosing was based on body surface area. Unfortunately, the effect of younger age versus relative underdosing cannot be distinguished by the design of the aforementioned studies.

As a consequence of all these uncertainties, the interesting results of Saadeh et al. [1] need confirmation by larger randomized prospective studies over longer periods of time before it can be certain that relative small dose differences are responsible for the frequency of relapses.

Is the target organ for immunosuppressive treatment in NS the immune system or the podocyte?

Until recently steroid-sensitive nephrotic syndrome was assumed to be an immune-mediated disorder. T–cell as well as B-cell abnormalities were believed to be the likely culprits, but the exact molecular mechanisms have not yet been deciphered. This topic has been well reviewed in an recent article written by Elie et al. in *Pediatric Nephrology* [10]. The concept of—and belief in—an immune-mediated disorder has favored the idea of an urgently required 'immunosuppressive hammer therapy' for the prevention of relapses in subsequent years. Clinical experience based on the treatment of other immune disorders, such as lupus erythematosus, have certainly contributed to this concept. The initial corticosteroid treatment was intended to be as high as that which could be tolerated without severe toxic adverse events. Even steroid pulse therapy has been used when the NS did not go into remission within 4 weeks [11].

The successful additive treatment with cyclosporine A (CsA) in SD NS and SR NS has provided further support for the concept of NS as an immune disorder. Initial treatment of NS with glucocorticoids combined with CsA was investigated in a prospective randomized trial [9]. Interestingly, the add-on of CsA led to a delay of early relapses, but after 2 years the effect was no longer visible.

More recently, focus has been directed towards primary defects of the podocyte cytoskeleton as pathogenetic factors of NS. For several years, lively discussions have been held on the question of whether circulating factors which might be produced by T-cells or immature cells are causal factors in proteinuria [12]. A two-hit podocyte disorder is currently hypothesized for the idiopathic NS [13]. The initial hit is believed to be the infection-induced induction of CD80 on the podocyte, which results in actin disturbance and proteinuria. Under normal conditions, CD80 expression is only transiently expressed on stressed podocytes. In minimal change nephrotic syndrome, however, a defect is postulated in CD80 podocyte autoregulation.

The majority of SD NS and of SR NS cases are based on genetic abnormalities of the podocyte. However, some of these patients do respond to treatment with corticosteroids plus CsA. In these cases, it is interesting to note that the

targets of CsA in glomerular disorders are not only T- or B-cells but also the podocyte cytoskeleton via inhibition of synaptopodin phosphorylation [14]. Stabilization of the cytoskeleton might be the explanation for the effects of add-on CsA observed in the APN CsA study [9]. The authors commented that the clinical effect of CsA lasted much longer than the immunosuppressive effects, suggesting a direct effect on podocyte stabilization.

Similar stabilizing effects on the podocyte cytoskeleton have been reported for mizoribine [15] and calcimimetic agents [16]. Likewise, glucocorticoids also seem to have a direct protecting effect on stressed podocytes [17]. Glucocorticoids limit podocyte damage and enhance their recovery by stimulating the expression of mitochondrial genes, resulting in the production of ATP and synthesis of fully glycosylated nephrin.

Molecular mechanisms for the action of corticosteroids in NS

The pharmacology and pharmacodynamics of glucocorticoids are not fully understood, and both genomic and non-genomic actions have been described. It is widely believed that the main effects of glucocorticoids act through the regulation of nuclear gene expression. Glucocorticoids are lipid-soluble molecules which can easily pass through cell membranes. Their effects are mediated primarily by the cytosolic glucocorticoid receptor (GR), which is activated, translocates to the nucleus, dimerizes, and finally activates anti-inflammatory genes (transactivation), such as interleukin-10. The GR also represses pro-inflammatory genes (trans-repression) by binding and inhibiting transcription factors such as nuclear factor kappa beta (NFkB). For more details on the mechanisms, the reader is referred to the articles of Elie et al. [10) and Groeneweg et al. [18]. Glucocorticoids can modulate gene activity further by protein–protein interaction and by regulation of mRNA stability. The clinical relevance of these mechanisms is not yet known. All these processes take several hours (range 4–24 h).

In more recent years, researchers have gained a better understanding of the non-genomic actions. These are independent of nuclear gene transcription and characterized by a rapid onset (seconds to minutes) and short duration (a few hours). Similar to the genomic effects, the non-genomic effects are dose-dependent.

One mechanism is the interaction with the cell membrane, resulting in an interaction with transmembrane mineral transport, such as calcium flux [18]. At high glucocorticoid doses, this mechanism contributes to the suppression of T-cell functions. Rapid T-cell immunosuppression is also mediated through the membrane-bound GR. The blocking of leukotriene production via binding to cytosolic GR is another non-genomic action.

The main genomic action of glucocorticoids in asthma seems to be trans-repression of proinflammatory transcription factors, but important non-genomic actions, such as rapid vascular effects, are also known [19]. In contrast, to date, no specific investigations have focused on the genomic and non-genomic effects in NS.

Can we individualize glucocorticoid therapy in patients with NS ?

It is assumed that most adverse events of treatment with glucocorticoids, such as Cushing syndrome, are mediated by the regulation of gene expression. It is unclear, however, why some patients are more resistant to adverse events than others. Insensitivity to glucocorticoids is only rarely explained by genetic variants of the GR [20]; more likely causes are reduced glucocorticoid binding to GR, reduced GR expression, enhanced activation of inflammatory pathways, or the lack of corepressor activity [21]. Other mechanisms, such as postreceptor tissue resistance, are also certainly involved [22].

The adjustment of glucocorticoid dosing to control adverse events would be a reasonable therapeutic concept if the therapeutic and adverse effects are equally mediated by the same molecular mechanisms. However, such an approach has not yet been approved. Aiming for the most effective high doses has led nephrologists to tolerate severe adverse events in individual patients for decades.

The group of Holmberg [23] has recently reported that there is no correlation between methylprednisolone (MP) dose (mg/kg) and adrenal suppression or growth in children with solid organ transplants. In contrast, the area under the serum MP time versus concentration curve (AUC) and, to an lesser extent, corticoid-bioactivity were good predictors of adrenal suppression, obesity, and growth. The authors concluded that dosing adjusted to serum MP AUC might have the potential to reduce the incidence of adverse events without affecting therapeutic targets.

In patients with NS, surprisingly little is known about the glucocorticoid binding protein (GCBP), which regulates glucocorticoid pharmacokinetics [24]. However, this binding protein might be lost with the development of proteinuria.

Several attempts to measure the variation in corticosteroid effects and to individually monitor therapy have been reported in recent years. These include the establishment of a sensitive assay for the determination of corticosteroid bioactivity [25], the monitoring of GR changes in peripheral blood mononuclear cells in kidney transplant recipients [26], and the monitoring of corticosteroid response by the effect of serum on signaling pathways of target immune cells in children with inflammatory bowel disease [27].

Conclusion

Corticosteroids act via many genomic and non-genomic pathways in NS. Similar to other immunosuppressive drugs, corticosteroids do not act only on the immune system but also directly on the podocyte cytoskeleton. The doses required for stabilization of the cytoskeleton may actually be lower than those needed for immunosuppression. The sensitivity to corticosteroids varies from patient to patient. Only when we have acquired more detailed information on the pathogenesis of NS and on the molecular mechanisms of the action of immunosuppressive drugs, we will be able to effectively study which drug, doses, and treatment duration are most effective for different forms of NS in different age groups. The finding of Saadeh et al. [1] that dosing of glucocorticoids per body surface area is superior to dosing per kilogram body weight (BW) in terms of reducing the recurrence rate of NS does not exclude an effect of age. Individualization of glucocorticoid treatment should be a target for future studies.

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