Consequences of disease and treatment in ANCA-associated vasculitis

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Chapter five

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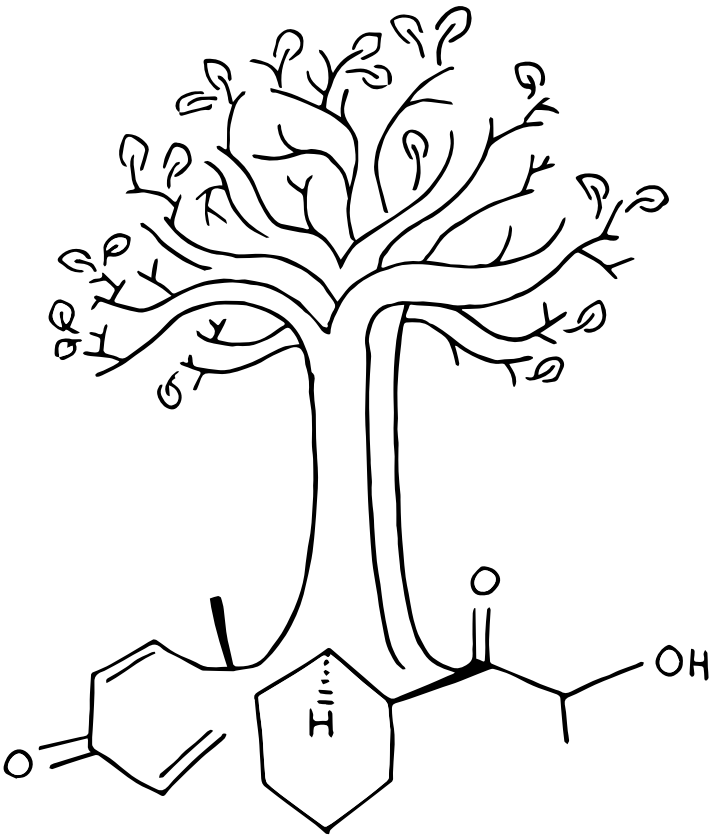

VIEWPOINT

Tapering of glucocorticoids in ANCA-associated vasculitis: one size does not fit all

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Abstract

Glucocorticoids have been a mainstay in the treatment of ANCA-associated vasculitis (AAV) and other rheumatologic diseases for many years. However, the optimal duration and dosage of therapy have not been established. Research is on the way to add to the body of knowledge regarding these aspects. Even less is known about the optimal regimen to withdraw glucocorticoids. Clinical experience shows that a considerable number of patients do not tolerate tapering well and a part of patients included in trials with a zero glucocorticoid target fail to reach this end-point, and therefore remain glucocorticoid dependent. Whether this is due to ongoing disease activity, failure to achieve adequate adrenal function after suppressive doses of glucocorticoids or other reasons remains unanswered. In spite of this, tapering regimes are not high on the research agenda.

Many questions therefore remain: what is the reason for differences in tapering? Might secondary adrenal insufficiency explain difficulties in tapering? What is the role of glucocorticoid sensitivity?

We aimed in this viewpoint to add new insights and developments which are relevant to the discussion on optimal glucocorticoid therapy, focussing on glucocorticoid tapering and with a critical view on glucocorticoid sensitivity.

Glucocorticoids in AAV

Glucocorticoids play a central role in the treatment of ANCA-associated vasculitides (AAV) as in many inflammatory or auto-immune diseases. AAV were almost invariably fatal before the introduction of glucocorticoids in the fifties. Their introduction increased survival up to 34% at one year [1]. Survival further improved after the addition of cyclophosphamide to a current 5-year survival rate of 78% to 83% [2, 3]. Standard therapy in AAV include high dose glucocorticoids as part of the induction treatment besides cyclophosphamide, or even new therapies like rituximab. Despite its importance, optimal duration and dosage are still unknown and treatment protocols vary widely. In clinical trials tapering regimes vary from 6- 27 months as shown in the overview of Walsh and colleagues [4]. Clearly no international consensus exists to date.

In rheumatoid arthritis (RA) it is stated that long-term low-dose glucocorticoids (< 5mg/day) is beneficial on outcomes in RA [5]. It has shown to retard the progression of joint damage and increase remission rates in RA [6]. In addition, it is postulated that low-dose glucocorticoid therapy has an acceptable low level of harm. However, AAV have a different aetiology and a beneficial effect of glucocorticoid treatment duration and intensity on relapse rate has not yet been proven in prospective trials. Only one meta-analysis suggested a beneficial effect on relapse rate with prolonged low-dose glucocorticoid treatment [4]. In contrast, one retrospective study and one randomized controlled trial showed no beneficial effect on relapse rate, but prolonged glucocorticoid therapy was accompanied by more adverse events and a greater incidence of infections [7, 8].

Side-effects and potential permanent damage limit the therapeutic benefits of glucocorticoids. Metabolic complications, cardiovascular disease and infections are a major concern not only during but also after glucocorticoid therapy for AAV. Deaths within the first year of AAV are primarily from infections (48%) and not the result of active vasculitis (19%). After the first year, cardiovascular disease (26%), malignancies (22%) and infections (20%) are the primary causes of death [2]. Besides mortality, AAV carry a high burden of morbidity. Hypertension (42%), osteoporosis (14%), malignancies (13%) and diabetes mellitus (10%) were the most prevalent treatment-related forms of damage at long-term follow-up after six EUVAS RCTs [9]. This is in line with the findings of the WGET study, in which hypertension, diabetes mellitus, significant muscle atrophy or weakness, osteoporosis or vertebral collapse and cataract were all reported in 5-10% of patients after a median follow-up of two years [10]. Glucocorticoids may have played an important role in the development of these forms of damage and may have contributed to susceptibility to infections. Subgroup analysis of the EUVAS trials revealed that increased cumulative glucocorticoid use was independently associated with higher levels of damage and having cataract and hypertension. Patients with longer duration of glucocorticoid treatment were more likely to have severe damage as defined by a Vasculitis Damage Index (VDI) of 5 or more, which has been associated with a six-fold increase in mortality [11, 12]. It should be acknowledged that with adjustment for disease severity and relapse rate confounding through more severe or more frequent disease activity on damage may still be present in this study. Still, the nature of reported damage strongly advocates a role for glucocorticoids therein.

Thus, the benefits of treatment should be weighed against the potentially adverse events and risk of irreversible damage. To prevent (progression of) damage tapering and withdrawal of glucocorticoids should be strived for in the majority of AAV patients.

Tapering of glucocorticoids

It is widely recognized that the optimal duration of therapy is unknown. As a result, new trials are underway to examine therapy duration with optimal disease control and the least possible side-effects (clinicaltrials.gov TAPIR NCT01933724; PEXIVAS NCT00987389) [13, 14]. In addition, glucocorticoid-sparing therapies like C5a receptor inhibitors are being studied to completely replace or reduce the doses of glucocorticoids needed (clinicaltrials.gov NCT01363388) [15]. However, less attention has been paid to the tapering itself, while this deserves more attention in order to reduce treatment toxicity.

In literature, problems during tapering are not systematically reported. However, a considerable part of patients do not discontinue glucocorticoids within the time frame of several studies or guidelines [7, 16]. A little less than 10% was not able to discontinue glucocorticoids within 6 months in the RAVE trial while in another study almost half of the patients did not discontinue glucocorticoids within 6 months according to their local protocol [7, 17]. It is striking that 25% of patients included in the CYCLOPS study still received glucocorticoids 4 years after study entry [18]. Similarly, subgroup analyses on the EUVAS trials showed that 21% of patients used prednisolone 3 to 4.5 years and 28% of patients used prednisolone for the duration of 5 years [11]. These observations make it evident that for whatever reason, many physicians and patients will fail to adhere to the treatment protocols.

In general, the initial glucocorticoid dose during induction treatment will be around 1 mg/kg/day prednisolone. Patients with severe disease may start with methylprednisolone 1000 mg for three consecutive days and switch to oral glucocorticoids thereafter. Tapering is usually initiated 2-6 weeks after initiation of therapy and normally a daily dose of 10 mg is reached within 4-5 months. After this point, great protocol variation is observed international. Our local protocol leads to glucocorticoid discontinuation within 7 months. Currently, we conduct a study to monitor recovery of HPA axis function during tapering from 10 mg to complete withdrawal (Dutch Trial Register NTR4966). During tapering the patients with AAV is observed for signs and symptoms of disease reactivation and dose reduction may be postponed or glucocorticoid dose may be increased. Further tapering after a long period on glucocorticoids should be performed carefully in order to prevent reactivation of disease on the one hand and prevent adrenal insufficiency to occur on the other.

At a certain point during tapering the 'physiological glucocorticoid dose' will be reached. At this point, especially after a long period on exogenous glucocorticoid (relative) adrenal insufficiency may occur due to a hypo-functional HPA axis. However, the dose which can be considered physiological is highly controversial. Some studies suggest that 7.5 mg of prednisolone and the bio-equivalent of 30 mg of hydrocortisone are physiological. This is based on cortisol production rate estimates in healthy individuals and in primary adrenal insufficiency this is thought to substitute the daily need [19]. Within patients with functional HPA axis a dose of 7.5 mg is not likely to result in full suppression of the endogenous cortisol production and the fusing of (partially) suppressed endogenous cortisol with the exogenous glucocorticoids cannot be considered physiological. To what extent exogenous glucocorticoids exert a suppressive effect on the HPA axis is difficult to predict. Some studies have shown that even low-dose glucocorticoids (<5mg/day) for a short period of time can result in impaired adrenal function [20]. HPA axis function varies widely when doses 5- 7.5 mg and higher are discontinued [21, 22]. These findings are supported by a meta-analysis and a recently published

systematic review, both showing a high incidence of adrenal insufficiency after glucocorticoid therapy but no dosing, no therapy duration or route of administration could be identified for which the occurrence of adrenal insufficiency could be safely excluded [23, 24]. Therefore, the occurrence of adrenal insufficiency cannot be predicted reliable based on these factors.

Further considerations while tapering are age and ethnicity. Clearance of glucocorticoids declines with ageing and Afro-Americans were shown to have slower glucocorticoid clearance and an increased frequency of adverse effects [25, 26].

Lastly, the circadian rhythm of the HPA axis should be considered while tapering. Synthetic glucocorticoids do not mimic the circadian rhythm of the HPA axis with high cortisol levels early in the morning and a low level during the evening and early night. In this view alternate-day dosing have been suggested to be beneficial, though clear evidence for this is lacking. Long-term suppression of the HPA axis may be the consequence of disruption of the circadian rhythm especially when bed-time doses of glucocorticoids are used [27].

It should be noted that glucocorticoids are involved in numerous processes and the effects of glucocorticoids are not restricted to the HPA axis necessarily. Other hormonal axes and systems such as the gonadal axis and proopiomelanocortin (POMC) derived peptides like β-endorphin are known to be affected [28, 29]. β-endorphin plays a role in pain mediation and mood[30]. Studies have shown that glucocorticoid administration suppresses β-endorphin production and increases pain perception in humans[28, 31]. To our knowledge, the effect of long-term suppression and subsequent tapering of glucocorticoids on pain mediation and mood via β-endorphin have not been investigated. It is interesting to speculate whether low levels of β-endorphin may play a role in pain and symptom perception during tapering after high-dose long-term glucocorticoid therapy.

It is also suggested by Hochberg and colleagues that a general withdrawal syndrome could account for some of the complaints experienced during glucocorticoid therapy [32]. Complex interactions between the HPA axis, the amygdala and the dopaminergic and noradrenergic system was hypothesized to be the underlying mechanism. According to this hypothesis, symptoms during tapering may be due to dysregulation of the central nervous system or due to inadequate glucocorticoid levels for other endocrine organs to function, though hard evidence is lacking.

In our experience, tapering of glucocorticoids can be challenging. A substantial number of patients report complaints while tapering, especially at lower doses of glucocorticoids (~2.5- 7.5 mg/day) or early after withdrawal. There appears to be a high inter-individual variation with respect to tapering, whereas some patients tolerate tapering well, others do not. The majority of these complaints are non-specific, like arthralgias, myalgias, malaise and fatigue, and difficult to distinguish from AAV disease activity. Most of these complaints promptly resolve after increasing the dose of glucocorticoids. This gives rise to the hypothesis that some patients may have developed a chronic central adrenal insufficiency, but with glucocorticoid levels that are high enough to prevent an adrenal crisis. Similar complaints after tapering in concordance with subnormal adrenal tests have already have been described by Graber in 1965 [33].

The high inter-individual variation with respect to glucocorticoid tapering has not yet been elucidated. As described above, neither dosing, nor duration can fully predict the extent of HPA axis suppression. As already suggested by Livanou in the Lancet in 1967, a factor of individual sensitivity to suppression by corticosteroids appears to be involved [21]. This is supported by the study of

Neidert who showed that cortisol levels after a dexamethasone suppression test were predictive for the development of adrenal insufficiency 7 days after discontinuation of a two-week course of high-dose prednisolone therapy [34]. This suggests that glucocorticoid sensitive individuals have a higher susceptibility for adrenal insufficiency. It will not come as a surprise that this glucocorticoid sensitivity not only affects tapering, but all aspects of glucocorticoid therapy, including the development of side effects and therapy success.

Glucocorticoid sensitivity

Research on glucocorticoid sensitivity is a rapidly growing field. The complexity of glucocorticoid regulation is impressive, partly due to the involvement of glucocorticoids in a myriad of metabolic and immune-modulatory processes. Due to their involvement in numerous mechanisms, small variations at different levels of regulation might eventually result in larger effects in the end. Glucocorticoid sensitivity has been extensively discussed by Quax et al and more recently by Ramamoorthyand and Cidlowski [35, 36]. Here, we briefly outline some important levels of glucocorticoid regulation giving rise to varying glucocorticoid sensitivity.

Glucocorticoid availability is regulated by cortisol binding globulin (CBG) and albumin. Approximately ninety per cent of endogenous cortisol is bound by CBG and albumin leaving 10% as free and therefore biologically active [37]. The affinity of synthetic glucocorticoid to CBG varies. Prednisolone competes with cortisol for binding sites of the CBG, while dexamethasone does not bind to CBG at all [38]. It is now evident that tissue levels of free cortisol are buffered by two responsive plasma pools, intact CBG with a high binding-affinity and, particularly in inflammation and sepsis, a further pool of cleaved-CBG with a ten-fold lower affinity. Another insight, is that the proteolytic cleavage of CBG in inflammation results in a partial loss of cortisol binding, (thus offering a targeted release of cortisol at the right place [39].

Glucocorticoids are lipophilic and enter the cells through passive diffusion. Subsequent binding of glucocorticoids to the intracellular glucocorticoid receptor (GR) is partly direct and partly regulated by the enzymes 11β hydroxysteroid dehydrogenase (11β-HSD) type 1 and 2 [40]. 11β-HSD1 mainly metabolizes inactive cortisone to bioactive cortisol [41]. 11β-HSD 2 can only convert cortisol to cortisone [42]. They exert counterbalancing actions and over- or underexpression of one of the two will affect glucocorticoid availability to the receptor. For example, overexpression of 11β-HSD1 in adipose tissue of mice is associated with insulin resistant diabetes and hyperlipidemia [43]. The importance of 11β-HSD1 is underlined by a clinical observation of a patient with pituitary-dependent Cushing's disease that did not develop the phenotypically characteristics. A defect in the function of 11β-HSD1 was found to be the underlying cause for the absence of symptoms [44]. This observation

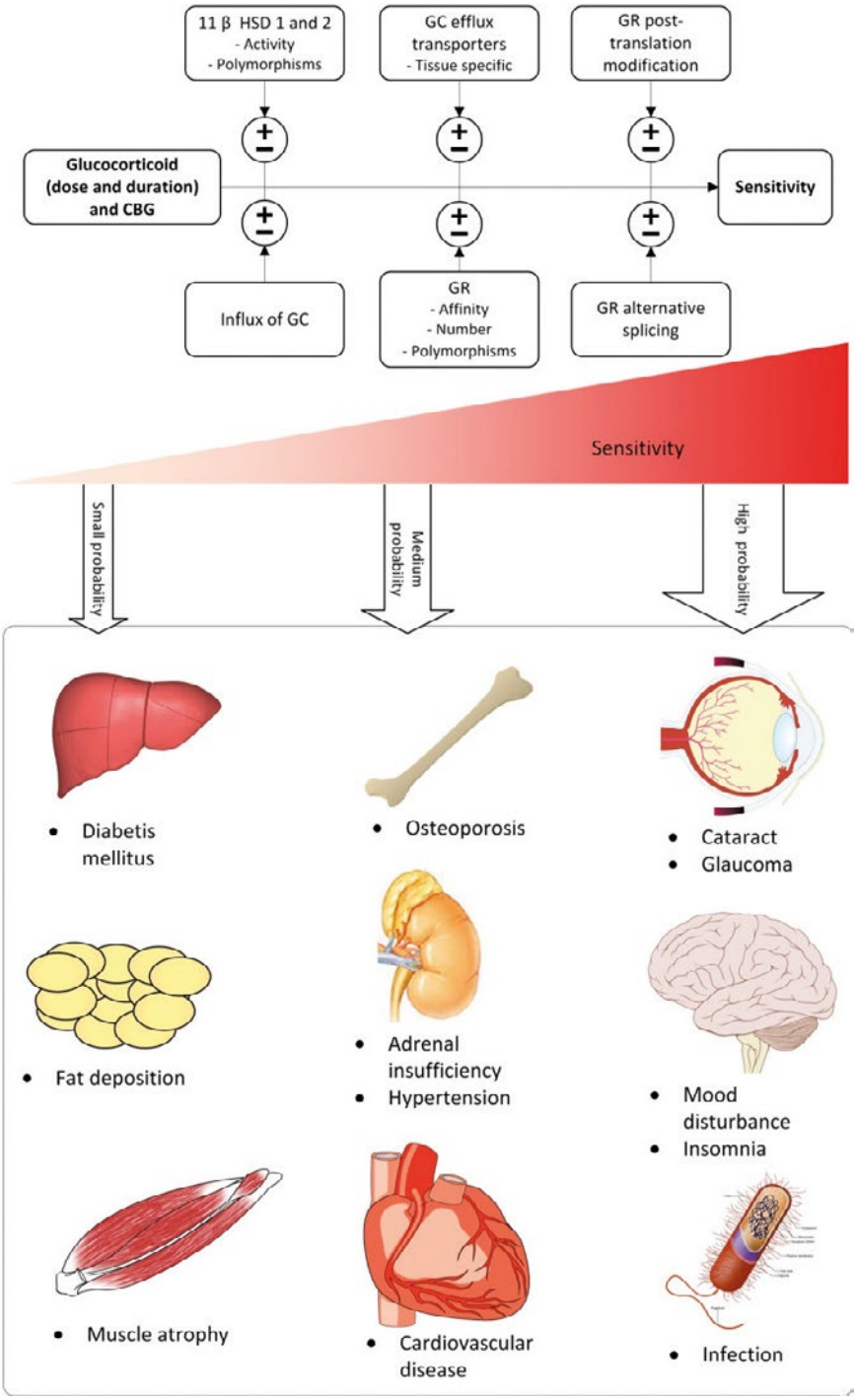

Figure 1. Glucocorticoid regulation and the hypothesized relation between glucocorticoid sensitivity and outcome.

was reproduced in 11β-HSD1 knock-out mice, whom were protected against the phenotypical and metabolic side effects of excess glucocorticoids [45]. This suggests that the direct activation of the glucocorticoid receptor by cortisol might be subordinate to metabolization of inactive cortisone or prednisone by 11β-HSD1. Polymorphisms of the gene encoding for the 11β-HSD1 and 2 enzymes may contribute to differences in cortisol regulation and have been shown to be associated with for example essential hypertension, bone mineral density, and cognitive function [46-48]. Tissue-specific up and down regulation of 11β HSD 1 and 2 further influences glucocorticoid bioavailability and enables tissue-specific glucocorticoid availability.

The glucocorticoid receptor adds to the complexity of glucocorticoid regulation. Studies suggest that that the number and affinity of available binding sites for glucocorticoids to the GR vary within the healthy population [49]. Alternative splicing of the gene coding for the glucocorticoid receptor leads to multiple GR isoforms which have independently been associated with several diseases and glucocorticoid resistance [50]. Additional alternative translation to translational isoforms give rise to more heterogeneity. These translational isoforms are thought to regulate distinct sets of genes.

Lastly, glucocorticoid receptor polymorphisms result in increasing or decreasing glucocorticoid sensitivity in individuals [51]. This has been shown in multiple clinical studies to result in clinically relevant effects on body mass index, bone mineral density, fasting insulin levels and muscle mass, strength and duration of adrenal insufficiency within patients with various diseases and the healthy population [36, 52]. An overview of the hypothesized relation between glucocorticoid sensitivity and outcome is shown in Figure 1.

Conclusion

The optimization of glucocorticoid treatment for the treatment of AAV receives increasing attention. Current evidence points to an important influence of glucocorticoids in the development of morbidity after the diagnosis of AAV. On the contrary, evidence that supports favourable outcome with long-term glucocorticoid treatment is lacking, or at best scarce. In that view we would state that complete glucocorticoid withdrawal should be aimed for within 6 to 12 months after therapy initiation.

Within this growing research field, much is still unknown, especially about tapering and withdrawal. A high inter-patient variation is observed with respect to tapering and complaints are frequently reported. We hypothesize that to a great extent the HPA axis is involved in the problems encountered during tapering of which the role of glucocorticoid sensitivity (a broad term which includes pharmacokinetics, chronotherapy, enzyme activity, and gene polymorphism) appears important.

This offers opportunities to individualize treatment in the future. Patient-tailored therapy which considers glucocorticoid sensitivity could be physiological more sound and might show better outcome in terms of efficacy, occurrence of side-effects, damage and the development of secondary adrenal insufficiency.

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