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SYSTEMATIC REVIEW

Pharmacokinetics and Pharmacodynamics of Systemic Corticosteroids in Autoimmune and Inflammatory Diseases: A Review of Current Evidence

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Abstract

Background and Objective Systemic corticosteroids have a long history of use in the treatment of autoimmune and inflammatory diseases. Both efficacy and safety show large interindividual variability (IIV), suggesting that corticosteroids may have the potential for individualised dosing strategies to optimise therapy. This systematic review aims to provide an overview of current evidence on the pharmacokinetic (PK) and pharmacodynamic (PD) relationships of systemic corticosteroids in patients with autoimmune and inflammatory diseases.

Methods A systematic literature search was conducted in PubMed and Embase for PK/PD studies of systemic corticosteroids in autoimmune and inflammatory diseases in humans published until December 2023. Studies were scored from 1 to 5 according to criteria for the levels of evidence, as inspired by the Oxford Centre for Evidence-Based Medicine.

Results Twelve studies (1981–2016) were included. The majority of these studies had a small sample size. The corticosteroids involved were prednisone, prednisolone, methylprednisolone and budesonide. Substantial IIV of corticosteroid PK was described in all studies. Evidence for a relationship between the PK of corticosteroids and efficacy was inconclusive and limited. However, there was some evidence for a relationship between the PK of prednisolone and the severity of Cushingoid features.

Conclusion There is insufficient evidence to draw firm conclusions on the potential associations between PK and clinical outcome of systemic corticosteroid treatment in autoimmune and inflammatory diseases. This is remarkable given the many decades that steroid drugs have been used in clinical care. Prospective research is recommended with robust and well-defined cohorts to fully quantify the PK/PD associations of corticosteroids.

1 Introduction

Corticosteroids are widely used in various autoimmune and inflammatory diseases due to their anti-inflammatory and immunosuppressive properties. Systemic corticosteroid treatment is generally highly effective and therefore the cornerstone treatment in diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), nephrotic syndrome (NS), myositis and inflammatory bowel diseases (IBD) [1–3]. However, corticosteroid-refractory disease has also been described, mostly in ulcerative colitis and graft versus host disease [4–7]. In addition, corticosteroid treatment is frequently accompanied by metabolic, cardiovascular and mental adverse events, with symptoms such as Cushingoid features, hypertension, diabetes, obesity and neuropsychiatric changes [1, 8–11]. Therefore, there seems room for improvement of efficacy for some diseases, while for others, the main concern of corticosteroid treatment is the (long-term) toxicity.

Corticosteroids are lipophilic moieties and generally well absorbed after oral administration [12]. Bioavailability ranges from 60 to 90% for dexamethasone and from 80 to 100% for hydrocortisone, (methyl)prednisolone and prednisone. In contrast, oral budesonide has a very low bioavailability of approximately 10%, due to P-glycoprotein-mediated efflux in the gastrointestinal tract and extensive first-pass metabolism via cytochrome P450 in the gut wall and liver [13]. Therefore, it is used for its local anti-inflammatory effect on gastrointestinal tissue, with the hypothesis of minimal systemic steroid-related side effects. Intravenous corticosteroids are administered as a hydrophilic phosphate or succinate for stability, and

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Key Points

This review revealed limitations of the current evidence on the pharmacokinetic (PK) and pharmacodynamic (PD) relationships of systemic corticosteroids in patients with autoimmune and inflammatory diseases.

Corticosteroids are still a widely used immunosuppressant with highly empirical dosing regimens, despite that steroid-refractory disease as well as steroid-related toxicities remain major concerns with corticosteroid therapy.

A proper investigation into the potential associations between the PK/PD relationship of corticosteroids in immune diseases, considering both efficacy and toxicity outcomes, is highly needed.

are converted within 30 min after administration into the active form [12]. Corticosteroids show moderate plasma protein binding, mostly to albumin. Hydrocortisone and prednisolone also bind with high affinity to corticosteroid binding globulin (CBG, or transcortin). However, plasma concentrations of CBG are relatively low, resulting in saturation of binding at corticosteroid concentrations of about 400 µg/L. Therefore, hydrocortisone and prednisolone have non-linear pharmacokinetics (PK) (at doses > 20 mg), with the unbound fractions (f_{unb}) depending on total plasma concentration. On the other hand, albumin has a lower binding affinity for corticosteroids, but an excessive binding site capacity. This results in a linear binding of the corticosteroids methylprednisolone and dexamethasone to albumin, with a constant f_{unb} independent from the plasma concentration of the corticosteroid [12]. Volumes of distribution of the different corticosteroids are approximately 0.5 L/kg for hydrocortisone and 1–2 L/kg for the other corticosteroids. However, the volume of distribution of protein-unbound prednisolone is much larger, up to 4–5 L/kg. Elimination half-lives of corticosteroids are generally short, approximately 4 h for dexamethasone and 2–3 h for budesonide, hydrocortisone, (methyl)prednisolone and prednisone [12, 13]. However, the biological half-life of corticosteroids is much longer, with 12 h for hydrocortisone, from 18 to 36 h for (methyl)prednisolone and prednisone and up to 54 h for dexamethasone [14]. The biological half-life depends on the potency and binding affinity of the particular corticosteroid for the glucocorticoid receptor [14, 15].

Both large intra-individual and interindividual variability (IIV) in the PK of corticosteroids have been observed [16, 17]. In liver transplantation, dose–body weight (BW)-normalised prednisolone PK varied in the post-transplant phase, with 30% reduced total apparent prednisolone clearance in week 2–4 after transplantation compared with week 1 [16]. Moreover, variability in prednisolone PK was linked to sex- and race-related differences, the use of concomitant medication (oestrogens, cyclosporine A) and genetic polymorphisms in the MDR1 gene that codes for the P-glycoprotein efflux transporter [16, 18, 19]. Also, IIV in PK parameters seem to be related to age, origin of the disease and disease state [20–22]. A significant inverse correlation between prednisolone clearance and age was observed in children below the age of 12 years, compared with older children and young adults [20]. In addition, higher prednisolone f_{unb} were seen during the active phase of the disease compared with children and young adults with NS and IBD in remission [21, 23, 24].

Corticosteroids have a direct suppressive effect on the immune system and the hypothalamic-pituitary-adrenal (HPA) axis, with cortisol a biomarker for HPA suppression [12, 25–27]. Direct immune suppression manifests in a decrease in lymphocyte count and lymphocyte proliferation, phagocyte function and all kinds of cytokines, such as interleukins, interferons and tumour necrosis factor [12]. For the effect on lymphocytes, there is a proven relationship between the (in vitro) inhibitory effect of prednisolone and methylprednisolone on lymphocyte proliferation and clinical response in patients with glomerulosclerosis [28]. The grade of lymphocyte steroid sensitivity was a prognostic factor in clinical response to treatment. For the effect on cortisol, an inverse correlation between methylprednisolone exposure, as measured by the area under the concentration–time curve (AUC) and both cortisol AUC and the cortisol suppression ratio was observed [29]. Corticosteroid concentration at which the half-maximum (CE_{50}) suppressive effect can be expected varies between corticosteroids, due to differences in potency for the glucocorticoid receptor [12]. The mean CE_{50} at which lymphocyte suppression is observed is 125 µg/L and 10 µg/L for total and unbound prednisolone, respectively, and 10 µg/L for methylprednisolone. Concentrations are expected to fall below the CE_{50} within 12 h after low-dose administration, due to the short elimination half-lives of these corticosteroids. For cortisol suppression, the mean CE_{50} is ten times lower, with 10 µg/L and 1 µg/L for total and unbound prednisolone, respectively, and 1 µg/L for methylprednisolone.

From a clinical perspective, the suppressive effect of corticosteroids on the immune system manifests in a decrease in C-reactive protein and an improvement in blood sedimentation and disease-related clinical symptoms, such as fever, renal function, proteinuria, pain, stool and muscle strength. The latter examples are mostly expressed in disease activity scores. As direct suppressive effects of corticosteroids are not usually measured in routine diagnostics, associations

between the PK of corticosteroids and surrogate endpoints or biomarkers to reflect clinical outcome as a pharmacodynamic (PD) parameter are common [12]. As a PK parameter, exposure to corticosteroids is often reflected by the magnitude of the concentration (peak/maximum concentration [C_{max}]) and/or the duration of the exposure, expressed as AUC [15]. Clinical PD parameters to reflect treatment response vary largely, such as the change in disease parameters from baseline and time to remission, relapse or rejection. These kinds of PK/PD relationships have been described for several conditions with an indication for corticosteroids. For instance, low prednisolone and dexamethasone AUCs were associated with a higher incidence of rejection in kidney transplant recipients and a higher risk of relapse in patients with acute lymphoblastic leukaemia (ALL), respectively [30, 31].

In autoimmune disease and solid organ transplant treated with mycophenolic acid (MPA) and tacrolimus, PK/PD relationships have resulted in optimised and individualised AUC-targeted therapies [32, 33]. For MPA, a 12-h AUC > 35 mg·h/L was likely to result in better treatment response in patients with autoimmune disease, favouring PK-based individualised dosing compared with standard dosing [32]. For renal transplant recipients on tacrolimus, it was suggested that a 4-h target AUC of 150 µg·h/L provided favourable clinical outcome after transplantation [33]. The same accounts for ALL and other malignant or benign disorders treated with haematopoietic cell transplantation (HCT), where PK/PD relationships with drugs in the HCT condition regimen also resulted in PK-based individualised or model-based dosing [34–38]. For fludarabine, the PD marker 2-year event probability (graft failure-, relapse- and non-relapse-related mortality) was lowest at a cumulative fludarabine AUC of 20 mg·h/L [38]. Similar results were obtained for busulfan at a cumulative AUC of 80–100 mg·h/L [34]. Key findings of these studies were that variability in AUC may be reduced by individualised dosing strategies and/or therapeutic drug monitoring to improve survival after HCT.

For clinical toxicities as a PD parameter, high and frequent or prolonged prednisolone AUC and exposure to unbound prednisolone (AUC_{unb}) were associated with a higher incidence of metabolic, neuropsychiatric and cardiovascular adverse events [19, 39–42]. Moreover, the risk of infections and fractures was increased with the dose and duration of corticosteroid therapy [43–45]. Of note, only the f_{unb} of the corticosteroid can bind to the glucocorticoid receptor at the site of action and initiate a biological effect. Therefore, protein binding and measurement of the unbound concentration is relevant, in particular for prednisolone due to its non-linear PK [17].

Considering the above, systemic corticosteroids may have the potential for PK-based individualised dosing strategies, as was already suggested by others [16, 17, 30]. Optimising corticosteroid therapy may result in a reduction in steroid-related toxicities while maintaining or even improving treatment efficacy. This systematic review aims to provide an overview of the current evidence on the PK/PD relationship of systemic corticosteroids regarding efficacy and toxicity in patients with autoimmune and inflammatory diseases, including discussion on the intra-individual variability and IIV in corticosteroid PK.

2 Methods

2.1 Literature Search and Study Selection

A systematic literature search was conducted in PubMed and Embase for articles published until December 2023 using the following query structure: (("DISEASE"[Title]) AND ("DRUG"[Title]) AND ("OUTCOME"[Title/Abstract]) NOT ("EXCLUSION"[Mesh])).

For each database, a specific search was generated and converted accordingly. See the online resources 1 and 2 in the electronic supplementary material for the full PubMed and Embase queries, respectively.

Studies reporting the PK/PD of systemic corticosteroids in autoimmune and inflammatory diseases were eligible for inclusion. The eligibility criteria are shown in Table 1. Next to the systemic corticosteroids and diseases of primary interest, other corticosteroids that had a systemic effect (intended or not) were also included when found with the MeSH terms "Glucocorticoids" or "Corticosteroid". The same applied to other immune diseases found with the MeSH terms "Autoimmune disease" or "Autoimmune disorder" or "Immune-related disease" or "Immune-related disorder". The results were subsequently screened by title, abstract and full text, respectively. Relevant articles that were found via references of identified studies were also included.

2.2 Data Collection

Authors JM and SE extracted and crosschecked the following data from each included study: diagnosis, sample size, age, type of corticosteroid, route of administration, dosage regimen, sampling scheme, quantification method, PK parameters, clinical outcome (i.e. disease parameters, adverse events, serum cortisol), concomitant medication and findings regarding the intra- and interindividual PK and PK/PD relationship of corticosteroids.

2.3 Level of Evidence

Inspired by the Oxford Centre for Evidence-Based Medicine levels of evidence, 5 levels of evidence for PK/PD studies

Table 1 Eligibility criteria for selection of relevant articles

Inclusion criteria	Exclusion criteria
Research conducted on patients with an autoimmune or inflammatory disease or primary interest*	Research conducted on animals or in vitro
Research conducted on patients treated with systemic corticosteroids of primary interest**	Route of administration (systemic) other than oral or intravenously (i.e. intramuscular, intra-articular, intrathecal)
Research regarding pharmacokinetic parameters in relation to efficacy or toxicity parameters	Research solely describing the pharmacokinetic parameters of corticosteroids
English, full-text available manuscripts	Review articles, meta-analysis studies, methodology studies and conference abstracts
Research published in other languages if they could be translated properly	

*Crohn's disease, (dermato)myositis, encephalitis, engraftment syndrome, graft versus host disease, haemophagocytic lymphohistiocytosis, hepatitis, (juvenile) rheumatoid arthritis, lupus nephritis, mixed connective tissue disease, multisystem inflammatory syndrome, nephrotic syndrome, polymyalgia rheumatica, sarcoidosis, Sjogren, systemic lupus erythematosus, systemic scleroderma, ulcerative colitis, uveitis, vasculitis

**Dexamethasone, methylprednisolone, prednisolone, prednisone

Table 2 Levels of evidence [46, 47]

Level	Criteria
1	PK/PD relationship regarding AUC and/or C_{max} related to clinical outcome and/or toxicity, in a large population (> 50 patients)
2	PK/PD relationship regarding AUC and/or C_{max} related to clinical outcome and/or toxicity, in a substantial population (21–50 patients)
3	PK/PD relationship regarding AUC and/or C_{max} related to clinical outcome and/or toxicity, in a small population (12–20 patients)
4	Case-report/series or pilot data on PK/PD in a very small population (≤ 11 patients) PK/PD relationship possibly influenced by concomitant drugs
5	Dose/PD relationship Mechanism-based reasoning Expert opinion

AUC area under the concentration–time curve, C_{max} peak concentration, *PD* pharmacodynamics, *PK* pharmacokinetics

were established [46, 47]. The criteria for the levels of evidence (scored from 1 to 5) are presented in Table 2.

3 Results

3.1 Literature Identification

A total of 4541 articles were identified after the removal of duplicates and screened on title and abstract (Fig. 1). Based on inclusion and exclusion criteria (Table 1), 15 relevant articles were eligible for full-text assessment. Subsequently, six articles were excluded based on the following: (1) two studies were PK studies without a relation to clinical outcome, (2) two studies only compared routes of administration of corticosteroids in relation to its efficacy or toxicity, (3) one study examined the influence of the disease state on the PK parameters and (4) one study assessed the relationship between PK and PD in a non-autoimmune hepatic disease. Three studies were identified and included after cross-referencing.

3.2 Study Characteristics

Twelve studies were identified as research investigating the relationship between PK parameters and efficacy or toxicity in patients with autoimmune and inflammatory diseases and included in this review. Substantiation of the level of evidence for each included study is shown in Table 3. Studies were published between 1981 and 2016 and consisted of both paediatric and adult patients with a variety of immune diseases, including Crohn's disease, lupus nephritis, SLE, NS, sarcoidosis and dermatomyositis. The corticosteroids involved were either prednisone, prednisolone, methylprednisolone or budesonide. Characteristics of each study, including the C_{max} and AUC as relevant PK parameters, outcome measurements and key points on PK and PK/PD are summarised in Table 4. Mentioned prednisolone concentrations are total C_{max} or total AUC, unless stated differently.

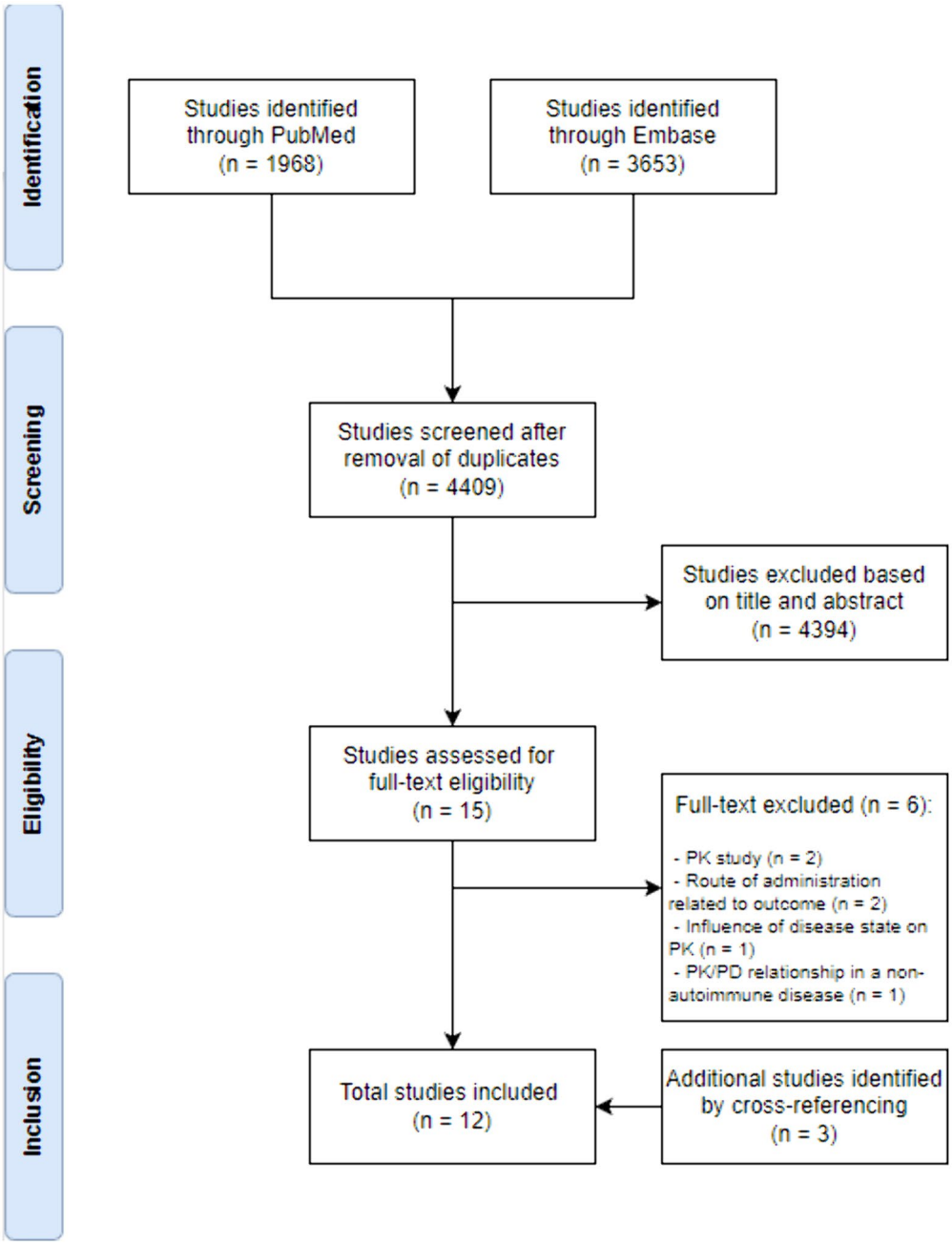

Fig. 1 PRISMA flowchart of study identification. *PD* pharmacodynamics, *PK* pharmacokinetics, *PRISMA* Preferred Reporting Items for Systematic reviews and Meta-Analyses

3.3 Pharmacokinetics in Adults and Paediatric Patients

Large IIV in corticosteroid PK was described in almost all studies [48–55]. For prednisolone, up to a 19-fold variation in AUC_{unb} and up to sixfold IIV in f_{unb} was observed in the therapeutic concentration range (100–300 µg/L) [48, 51]. Due to the saturable binding of prednisolone to plasma proteins, a twofold intra-individual variability in f_{unb} was seen within the dosage interval at steady state of long-term prednisone therapy [51]. As expected, linear prednisolone PK was observed in patients who used low doses (≤ 10 mg/day) [52]. However, dose-normalised trough concentration (C_{min}) varied sixfold in this study. Suggested explanations for these observed large IIV in prednisolone PK included variable absorption and metabolism-related variability, such as differences in the conversion of prednisone to its active metabolites, the potential role of known genetic polymorphisms in the MDR1 gene and effects of other drugs on metabolism [49, 55, 56]. In addition, it was suggested that this might explain the highly variable and even unpredictable

Table 3 Substantiation of the level of evidence of included studies

Reference	Level of evidence	Substantiation
Abd Rahman et al. (2015) [48]	2	PK/PD regarding AUC and C_{max} related to clinical outcome and toxicity in 25 patients
Baron et al. (1988) [50]	3	PK/PD regarding AUC and C_{max} related to clinical outcome and toxicity in 18 patients *Note:* PK parameters for C_{max} and AUC seem not plausible (10.000-fold higher compared with other studies)
De Silva et al. (1983) [52]	5	Dose/PD relationship
Dilger et al. (2006) [59]	5	Dose/PD relationship
Faure et al. (1998) [55]	3	PK/PD regarding AUC and C_{max} related to clinical outcome in 12 patients
Lipnick et al. (1992) [56]	4	PK/PD regarding AUC and C_{max} related to toxicity in 10 patients
Lundin et al. (2003) [57]	4	PK/PD regarding AUC and C_{max} related to clinical outcome and toxicity in ≤ 11 patients, since data in children ($n = 8$) were compared with adult data ($n = 6$)
Rostin et al. (1990) [53]	3	PK/PD regarding AUC and C_{max} related to clinical outcome and toxicity in 13 patients
Sagcal-Gironella et al. (2011) [49]	4	PK/PD regarding AUC and C_{max} related to clinical outcome in 8 patients
Teeninga et al. (2016) [54]	5	Mechanism-based reasoning; unbound serum prednisolone was estimated based on measurements in saliva and a previous model developed in healthy adults
Thompson et al. (1986) [58]	4	PK/PD regarding AUC related to clinical outcome and toxicity in 10 patients
Wagner et al. (1981) [51]	5	Mechanism-based reasoning; no direct association between PK and outcome. Protein binding was used as derivative of PK

AUC area under the concentration–time curve, C_{max} peak concentration, *PD* pharmacodynamics, *PK* pharmacokinetics

clinical response in patients receiving prednisolone in the therapeutic dosing range [51, 53, 54].

In general, PK parameters of corticosteroids did not differ between adults and children of different ages (after BW correction), diseases or disease states [55, 57–59]. For example, prednisolone PK in patients with sarcoidosis were comparable to healthy volunteers, patients with asthma and tuberculosis patients [58]. The same accounts for the PK of budesonide in children with Crohn's disease as compared with healthy adults [59]. Although the disposition of prednisolone was highly variable between individuals with IBD, this was not the result from differences in PK parameters between patients with active disease or in remission [55]. The high variability in clearance between children in this study was not related to age or severity of the active disease. On the other hand, in SLE patients, the prednisolone association constant for binding to CBG (k_{CBG}) was significantly lower compared with patients with asthma, and the association constant for binding to albumin (k_{alb}) was significantly lower compared with RA patients ($p < 0.025$) [51].

3.4 Associations Between Pharmacokinetics and Efficacy in Adult and Paediatric Patients

The relationship between corticosteroid PK and efficacy was addressed in nine of the 12 included studies [48–50, 52–55, 57, 58]. Overall, there was only limited and, therefore, insufficient evidence for such a relationship. In multiple studies, it was suggested that differences in corticosteroid PK were not a major determinant of drug response, but that unknown PD mechanisms or the heterogeneity in the pathogenesis of the disease might influence the efficacy of corticosteroids [50, 53, 55]. It should be noted that the studies included 25 patients or fewer, had a short follow-up period or were scored with the lowest level of evidence.

Three paediatric studies in patients with NS found no associations between the PK of prednisolone and either corticosteroid sensitivity or clinical outcome [50, 53, 54]. In a study with 18 patients, the PK of prednisolone did not differ between patients with rapid remission after treatment initiation and patients with slow remission, or remission with need for higher-level corticosteroid therapy (3 mg/kg prednisolone or methylprednisolone pulses) [50]. Also PK in patients with frequent relapses and need for high prednisolone dosing (≥ 0.5 mg/kg/day) did not differ from children with rare relapses who were treated with lower doses (< 0.5 mg/kg/day). Likewise, in 13 patients with a flare of NS, no association was found between the PK of prednisolone and the onset of the response after initiation of corticosteroid treatment [53]. In addition, no differences were found regarding prednisolone PK between patients with steroid-sensitive, steroid-dependant and steroid-resistant NS. Similarly, no relevant correlations were found between prednisolone AUC_{unb} and time to remission, total number of relapses, and relapses per year in 104 patients with NS in remission [54]. Prednisolone AUC_{unb} was similar in children with a first relapse compared to children who were in remission. Only a weak, borderline significant correlation was observed between AUC_{unb} and total number of relapses ($r_s = 0.19$) and a weak, but significant correlation was observed between AUC_{unb} and number of relapses per year ($r_s = 0.22$).

Table 4 Overview of PK/PD studies on corticosteroids in autoimmune diseases

Reference	Disease type (*n*)	Age (years)	Corticosteroid dosage regimen	Sampling time (h), PK dose and duration of therapy	C_{max} (µg/L)	AUC_h (µg·h/L)	Outcome measurement	Key findings on PK, PK-efficacy and PK-toxicity
Abd Rahman et al. (2015) [48]	Lupus nephritis ($n = 25$)	32.6 (22.4–45.6)[a]	*Standard therapy ($n = 18$):* Prednisolone PO 12.5 (10-22.5)[a] mg/day + MPA *Triple therapy ($n = 7$):* Prednisolone PO 10 mg/day + MPA + CsA	Pre-dose, 1, 2, 4, 6 and 8 PK after ≥ 4 weeks at stable dose: 10 (10–10)[a] mg Duration of therapy at time of PK was 0.7 (0.4–1.4)[a] years	*Responders* 217 (191–393)[b,k] $C_{max\ unb}$ 59 (42–81)[b,k] *Non-responders* 246 (211–359)[b,k] $C_{max\ unb}$ 64 (14–100)[b,k] *Cushingoid patients* 278 (238–358)[b,k] $C_{max\ unb}$ 79 (58–100)[b,k] *Non-Cushingoid patients* 230 (196–278)[b,k] $C_{max\ unb}$ 59 (42–81)[b,k]	*Responders* AUC_{0-24}: 1869 (1387–2418)[b,k] $AUC_{unb0-24}$: 316 (190–378)[b,k] *Non-responders* AUC_{0-24}: 1999 (1182–3013)[b,k] $AUC_{unb0-24}$: 453 (154–689)[b,k] *Cushingoid patients* AUC_{0-24}: 2369 (1848–3089)[b,k] $AUC_{unb0-24}$: 494 (51–639)[b,k] *Non-Cushingoid patients* AUC_{0-24}: 1834 (1387–2418)[b,k] $AUC_{unb0-24}$: 305 (190–378)[b,k]	*Primary* Treatment response *Secondary* Drug-related adverse events On the day of PK sampling	7-fold (CV 45%) and 19-fold (CV 54%) IIV in dose-normalised AUC_{0-24} and $AUC_{unb0-24}$ prednisolone, respectively 5-fold IIV (6.9–33.8%) in prednisolone f_{unb} C_{min} not useful for prediction of AUC due to short half-life No association between prednisolone AUC_{0-24} and $AUC_{unb0-24}$ and treatment response (defined as a ≥ 50% decrease in proteinuria, inactive urinary sediments and a normal or increased eGFR by 25%) Poorer treatment response in patients with lowest tertile AUC of both MPA and prednisolone compared with patients with middle and higher tertile AUCs (17% vs. 74%, $p = 0.023$) Higher prednisolone AUC and $AUC_{unb0-24}$ in patients with drug-related adverse events (2474 vs. 1615 µg·h/L, $p = 0.003$; 404 vs. 256 µg·h/L, $p = 0.029$, respectively) Higher prednisolone $AUC_{unb0-24}$ in patients with Cushingoid appearances ($p = 0.019$) Maintaining prednisolone $AUC_{unb} < 324$ µg·h/L may minimise corticosteroid-related adverse events in patients requiring prolonged therapy

Table 4 (continued)

Reference	Disease type (*n*)	Age (years)	Corticosteroid dosage regimen	Sampling time (h), PK dose and duration of therapy	C_{max} (µg/L)	AUC_h (µg·h/L)	Outcome measurement	Key findings on PK, PK-efficacy and PK-toxicity
Baron et al. (1988) [50]	NS ($n = 16$), RA ($n = 1$) and DM ($n = 1$)	6.4 ± 3.6[c,l]	Prednisolone PO 2 mg/LBW/day in 2 doses for 4 weeks, followed by reduction to alternate-day therapy for 2 months, slowly tapered over 2 months	Pre-dose, 0.5, 1, 2, 3, 4 and 6 (+8, 12 and 24 for $n = 6$) PK within 4 weeks on 1 mg/LBW (tapered) dose Duration of therapy at time of PK was 0.9 (0.5–8)[d,k] years	3250 ± 1300[c,k] *High steroid sensitivity* 3526 (1850–5500)[d,k] *Low steroid sensitivity* 3110 (1220–6110)[d,k]	47580 ± 15120 × 10^3 [c,k] *High steroid sensitivity* 4470 (3348–6390) × 10^4 [d,k] *Low steroid sensitivity* 4538 (2496–8118) × 10^4 [d,k]	*Primary* Corticosteroid sensitivity and drug-related adverse events *Secondary* Hypoalbuminaemia-related PK modifications and adverse events	5-fold IIV in C_{max} of prednisolone No effect of hypoalbuminaemia on the metabolism of prednisolone No correlation between PK parameters and corticosteroid sensitivity (defined as the time and dosage required to obtain and maintain remission) No differences in C_{max} between patients who tolerated their treatment well and those who did not Higher AUC in patients with poor prednisolone tolerance (defined as a score ≥ 3 on a scale of 0–11 for severity of corticosteroid-related complications) ($p < 0.05$) All participants with AUC < 3840 × 10^4 µg·h/L tolerated their treatment well compared with 40% of participants with AUC > 3840 × 10^4 µg·h/L *Note:* PK parameters for C_{max} and AUC seem not plausible (10- and 10.000-fold higher compared with other studies, respectively)
De Silva et al. (1983) [52]	RA ($n = 7$)	62 (42–74)[d]	Irrespective of pre-trial maintenance dose: Prednisolone PO 10 mg/day and reduced to 7, 6 and 5 mg/day in weekly intervals	Pre-dose, 1, 2 and 3 PK on every 7th day of 10, 7, 6, 5 mg dose Duration of therapy at time of PK was 5.8 (1–20)[d] years	10 mg: 349 ± 48[c,k] 7 mg: 325 ± 41[c,k] 6 mg: 263 ± 32[c,k] 5 mg: 171 ± 15[c,k]	10 mg: AUC_{0-24}: 2375[e,l] 7 mg: AUC_{0-24}: 2740[e,l] 6 mg: AUC_{0-24}: 2293[e,l] 5 mg: AUC_{0-24}: 1699[e,l]	*Primary* Treatment response (clinical and laboratory disease parameters) *Secondary* Fasting plasma cortisol On every 7th day	No correlation between prednisolone levels and articular index, grip strength, pain erythrocyte sedimentation rate and C-reactive protein A negative rank correlation between prednisolone dose and duration of morning stiffness ($p < 0.05$) HPA axis suppression was seen in patients with long-term prednisolone maintenance dose ≥ 7.5 mg, with cortisol levels < 276 nmol/L and little to no response to reduction in steroid dose

Table 4 (continued)

Reference	Disease type (*n*)	Age (years)	Corticosteroid dosage regimen	Sampling time (h), PK dose and duration of therapy	C_{max} (µg/L)	AUC_h (µg·h/L)	Outcome measurement	Key findings on PK, PK-efficacy and PK-toxicity
Dilger et al. (2006) [59]	Crohn's disease ($n = 12$)	12.9 ± 3.1[c]	Budesonide PO (MR) 3 mg/day on day 1, followed by 9 mg/day in 3 doses from days 2 to 8	Pre-dose, 1, 2, 2.5, 3, 4, 4.5, 5, 6, 8 and 24 PK on day 1 (initial start of therapy) and day 8 at 3 mg dose	*Single dose* 1.8 ± 1.2[c] *Steady state* 1.8 ± 1.1[c]	*Single dose* $AUC_{0-\infty}$: 7.7 ± 5.1[c] *Steady state* AUC_{0-8}: 6.7 ± 4.0[c]	PD action (cortisol levels, AUC_{0-24} and cumulative amount excreted in urine) On day 1 and 8	PK parameters of budesonide 3 mg single-dose did not change upon steady-state dosing PK parameters did not differ between children with Crohn's disease and healthy adults Reversible adrenal suppression was observed, with decreased morning plasma cortisol levels after 1 week of budesonide 3 mg trice daily ($p < 0.01$), most pronounced in children aged < 12 years
Faure et al. (1998) [55]	Crohn's disease ($n = 8$), recto colitis ($n = 3$) and undefined colitis ($n = 1$)	12.3 ± 3.0[c]	Prednisone PO 2 mg/kg during 48 h for PK, followed by 1–2 mg/kg/day depending on disease state	1, 2, 3, 4, 6, 8, 12, 18 and 24 PK after 2 mg/kg dose in the active phase and during remission *Note:* 7 out of 12 patients had corticosteroids at time of inclusion	*Responders* Active phase: 690 ± 210[c] Remission: 730 ± 410[c] *Non-responders* Active phase: 630 ± 160[c] Remission: 680 ± 230[c] (prednisolone)	*Responders* Active phase: $AUC_{0-\infty}$: 4110 ± 1320[c] Remission: $AUC_{0-\infty}$: 3070 ± 1250[c] *Non-responders* Active phase: $AUC_{0-\infty}$: 3900 ± 450[c] Remission: $AUC_{0-\infty}$: 3350 ± 810[c] (Prednisolone)	*Primary* Influence of disease state on PK *Secondary* Treatment response (PCDAI) On day 15	High IIV in clearance (0.98 ± 0.99 L/h/kg)[c], but not related to age, disease or severity of the active disease No differences in PK parameters of prednisolone in patients with active disease and when in remission (defined as a PCDAI < 30) No differences in PK parameters of prednisolone in responders and non-responders Treatment response to oral prednisone was 50%; 5 out of 6 non-responders required methylprednisolone IV to achieve remission

Table 4 (continued)

Reference	Disease type (*n*)	Age (years)	Corticosteroid dosage regimen	Sampling time (h), PK dose and duration of therapy	C_{max} (µg/L)	AUC_h (µg·h/L)	Outcome measurement	Key findings on PK, PK-efficacy and PK-toxicity
Lipnick et al. (1992) [56]	SLE ($n = 7$), juvenile RA ($n = 2$) and DM ($n = 1$)	13 (6–18)[d]	Patients' usual dose of prednisone PO (not specified)	Pre-dose, 0.5, 1, 1.5, 2, 4 and 6 No data on PK dose	*Cushingoid patients* 82[e] *Non-Cushingoid patients* 44[e] (Prednisolone)	*Cushingoid patients* AUC_{0-6}: 248[f] *Non-Cushingoid patients* AUC_{0-6}: 134[f]	Steroid activity (PE in relation to Cushingoid features)	Almost 2-fold higher C_{max} and AUC in Cushingoid patients (Cushing score ≥ 3) compared with non-Cushingoid patients (Cushing score < 3) (assessed on a scale of 0–5 according to the method of Bergrem [41]) Moderate to strong correlations between C_{max} and Cushing score ($r_s = 0.78$)[g], and AUC and Cushing score ($r_s = 0.72$)[g] No correlation between Cushing score and (1) cumulative dose, (2) disease activity or (3) total or unbound cortisol (peak or AUC).
Lundin et al. (2003) [57]	Crohn's disease ($n = 8$ children, $n = 6$ adults)	*Children* 12.4 ± 1.8[c] *Adults* 33.2 ± 12.6[c]	Budesonide 0.5 mg IV on day 1, followed by Budesonide PO (CR) 9 mg/day from day 2 to day 7	Pre-dose, 0.5, 1, 2, 3, 4, 6, 9, 12 and 24 PK on the 7th day at 9 mg dose	*Children* $2.6 \pm 1.5 \times 10^{-3}$ [c,k] *Adults* $1.7 \pm 0.9 \times 10^{-3}$ [c,k]	*Children* AUC_{0-24}: $17.8 \pm 9.1 \times 10^{-3}$ [c,k] *Adults* AUC_{0-24}: $15.1 \pm 8.5 \times 10^{-3}$ [c,k]	*Primary* Systemic exposure in children and adults *Secondary* Suppression of plasma cortisol On day 7	No differences in PK parameters between children and adults Systemic budesonide AUC and cortisol suppression similar in children (> 30 kg) and adults with active Crohn's disease No correlation between budesonide AUC and disease activity indices PCDAI and CDAI after a 7-day treatment period Non-significant plasma cortisol AUC decrease of 50 (18–89)[d] % and 64 (37–92)[d] % in adults and children, respectively Two patients with the highest budesonide AUC had the strongest plasma cortisol suppression

Table 4 (continued)

Reference	Disease type (*n*)	Age (years)	Corticosteroid dosage regimen	Sampling time (h), PK dose and duration of therapy	C_{max} (μg/L)	AUC_h (μg·h/L)	Outcome measurement	Key findings on PK, PK-efficacy and PK-toxicity
Rostin et al. (1990) [53]	NS ($n = 13$)	8.6 ± 4.6[c,l]	Prednisone PO 1 mg/kg/day	Pre-dose, 0.5, 1, 2, 3, 4, 6 and 8 PK on day 1 (initial start of therapy) at 1 mg/kg dose	325 ± 69.4[c] (Prednisolone)	AUC_{0-8}: 1330 ± 404[c] (Prednisolone)	Treatment response (criteria for clinical effectiveness) At 6 months	Moderate correlation between hypoalbuminaemia and prednisolone AUC (r_s = 0.60) and between hypoalbuminaemia and C_{max} (r_s = 0.72) No differences in prednisolone PK between steroid-sensitive, steroid-dependant and steroid-resistant NS No correlation between PK parameters and criteria of clinical effectiveness in NS (criteria not further defined)
Sagcal-Gironella et al. (2011) [49]	SLE ($n = 6$ children, $n = 2$ adults)	16.5 ± 5.3 (12–28)[c,d]	Prednisone PO 19.4 ± 11.5 (5–40) mg/day[c,d]	Pre-dose, 0.33, 0.67, 1, 1.5, 2, 3, 4, 6 and 9 PK after ≥ 30 days at stable dose: 0.29 ± 0.16 mg/kg/day[c]	287 ± 206 (124–712)[c,d] (Prednisolone)	AUC_{0-9}: 1094 ± 664 (467–2404)[c,d] (Prednisolone)	Treatment response (SLEDAI and BILAG) On the day of PK sampling	61% and 58% IIV in prednisolone AUC and dose-normalised AUC, respectively Non-significant relationship observed between dose-adjusted AUC_{0-9} and disease activity as measured by BILAG (preliminary results) No relationship established between dose-adjusted AUC_{0-9} and disease activity as measured by SLEDAI

Table 4 (continued)

Reference	Disease type (*n*)	Age (years)	Corticosteroid dosage regimen	Sampling time (h), PK dose and duration of therapy	C_{max} (µg/L)	AUC_h (µg·h/L)	Outcome measurement	Key findings on PK, PK-efficacy and PK-toxicity
Teeninga et al. (2016) [54]	NS ($n = 104$)	4.6 (3.3–6.5)[a]	Prednisone PO 60 mg/m^2/day for 6 weeks, followed by 40 mg/m^2 on alternate days for at least 4 weeks	Pre-dose, 2, 5 and 8 (+1 and 24 for $n = 16$) on the day of prednisolone intake PK after ≥ 4 weeks, during the 40 mg/m^2 alternate day treatment period	No data	3181 (2795–3834)[a] AUC_{unb}: 805 (688–977)[a] Remission: AUC_{unb}: 824 (700–948)[a] First relapse: AUC_{unb}: 904 (791–1183)[a] Cushingoid: AUC_{unb}: 859 (792–948)[a] Non-Cushingoid: AUC_{unb}: 864 (805–945)[a]	*Primary* Clinical outcome (remission and relapses) *Secondary* Drug-related adverse events Duration of follow-up: 3.9 (2.9–5.0)[a] years	Estimation of unbound serum prednisolone through non-invasive saliva measurements No relevant differences in AUC_{unb} between children with none to frequent relapses, with or without steroid dependence (defined as either ≥ 2 relapses within 6 months or ≥ 4 relapses within 12 months, and ≥ 2 consecutive relapses during or within 2 weeks after cessation of prednisolone, respectively) Prednisolone AUC_{unb} was similar in children with a first relapse compared to children who were in remission Weak correlation between AUC_{unb} and total number of relapses ($r_s = 0.19$) and between AUC_{unb} and number of relapses per year ($r_s = 0.22$) No differences in AUC_{unb} between Cushingoid and non-Cushingoid patients
Thompson et al. (1986) [58]	Sarcoidosis ($n = 10$)	25–68[i]	Single dose of prednisone PO 75 mg	Pre-dose, 0.33, 0.67, 1, 2, 3, 4, 6, 8, 12, 15 and 24 PK after single dose of 75 mg	No data	$AUC_{0–24}$: 5850 ± 397[j]	*Primary* Disease progress (ACE) *Secondary* Suppression of plasma cortisol On day 2	Prednisolone PK was comparable to healthy volunteers, asthmatic patients and tuberculosis patients No difference in serum ACE (biomarker) concentration after a single dose of 75 mg prednisolone within the 24-h study period Cortisol suppression was observed for at least 15 h after a single dose of 75 mg prednisolone

Table 4 (continued)

Reference	Disease type (*n*)	Age (years)	Corticosteroid dosage regimen	Sampling time (h), PK dose and duration of therapy	C_{max} (µg/L)	AUC_h (µg·h/L)	Outcome measurement	Key findings on PK, PK-efficacy and PK-toxicity
Wagner et al. (1981) [51]	Asthma ($n = 3$), SLE ($n = 8$), RA ($n = 3$), PSS ($n = 2$) and PAN ($n = 1$)	38.8 ± 19.8[c,l]	Prednisone PO 34.1 ± 16.5 (11–90) mg/day[c,d] Divided into 1–6 daily dosages	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24, dependant on the dosage interval PK after 14 (6–42)[a] days at dose: 34.1 ± 16.5 mg/day[c] Duration of therapy at time of PK was 0.8 (0.1–2.2)[a,k] years	360 ± 72[c,l] (Prednisolone)	No data	Drug-related adverse events (Cushingoid features) On the day of PK sampling	4- to 6-fold IIV in prednisolone f_{unb} in the therapeutic range (100–300 µg/L) SLE patients have a lower k_{alb} than patients with RA, and lower k_{CBG} than patients with asthma ($p < 0.025$) Non-significant higher k_{alb}, k_{CBG} and binding capacity for CBG to prednisolone in patients with Cushingoid features (all SLE patients) No correlation with either prednisone dose, nor duration of therapy and prednisolone plasma binding parameters No correlation between the occurrence of prednisone-induced adverse events and prednisolone plasma protein binding parameters

ACE angiotensin-converting enzyme, *alb* albumin, *AUC* area under the concentration–time curve, *BILAG* British Isles Lupus Activity Group, *CBG* corticosteroid binding globulin, *CDAI* Crohn's Disease Activity Index, C_{max} peak concentration, C_{min} trough concentration, *CI* confidence interval, *CR* controlled release, *CsA* cyclosporine A, *CV* coefficient of variation, *DM* dermatomyositis, *eGFR* estimated glomerular filtration rate, *f* fraction, *HPA* hypothalamic-pituitary-adrenal, *IIV* Interindividual variability, *IV* intravenous, *k* association constant, *LBW* lean body weight, *MPA* mycophenolate mofetil, *MR* modified release, *NS* nephrotic syndrome, *PAN* polyarteritis nodosa, *PCDAI* Paediatric Crohn's Disease Activity Index, *PD* pharmacodynamic, *PE* prednisolone equivalents, *PK* pharmacokinetics, *PO* per os, *PSS* progressive systemic sclerosis, *RA* rheumatoid arthritis, *SLE* systemic lupus nephritis, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index, *unb* unbound

[a]Median (interquartile range)

[b]Median (95% CI)

[c]Mean ± SD

[d]Mean (range)

[e]Mean

[f]Mean in dose-adjusted prednisolone equivalents

[g]Spearman's rank correlation coefficient (r_s)

[h]The duration of the concentration-time curve (ifknown), for example 0-24

[i]Range

[j] Mean (standard error of the mean)

[k] Unit conversion by authors JM/SE

[l] Calculated parameter by authors JM/SE (some studies provided corticosteroid concentrations, but did not calculate the relevant PK parameters and/or corresponding spreading)

In four other studies, with only a limited number of patients and various underlying immune diseases, no association was observed between corticosteroid PK and treatment response [48, 49, 52, 55]. In 12 paediatric patients with Crohn's disease, there were no differences in the PK parameters of oral prednisolone in the active phase and during remission and between responders and non-responders [55]. In this study, six children responded to oral prednisolone treatment, while six children did not, and 83% of these non-responders required intravenous methylprednisolone to achieve remission. Responders and non-responders were similar in age, localisation of the disease and albuminaemia. Similarly, in 25 adult patients with lupus nephritis, both the prednisolone AUC and AUC_{unb} did not differ between responders and non-responders [48]. Also no differences in PK parameters were found in responders receiving conventional (prednisolone + MPA) or triple therapy (prednisolone + MPA + cyclosporine A) and non-responders. However, a significant poorer treatment response was observed in patients with the lowest tertile MPA AUC and prednisolone AUC as compared with patients with middle and higher tertile AUC to both immunosuppressant drugs ($p = 0.023$). Likewise, in eight paediatric and adult patients with childhood-onset SLE, a preliminary analysis showed a potential, but non-significant inverse relationship between dose-normalised prednisolone AUC and disease activity, as measured by British Isles Lupus Assessment Group [49]. It should be noted that these patients also used MPA and hydroxychloroquine as concomitant immunosuppressants. Furthermore, in a pilot study in seven RA patients no correlations were found between prednisolone concentrations and most of the clinical or laboratory disease parameters studied [52]. However, they did find a negative correlation between the prednisolone dose and the duration of morning stiffness ($p < 0.05$). All patients deteriorated at some stage during steroid tapering. It was suggested that steroid tissue levels in the affected joints may be an important factor for treatment response in RA.

Lastly, two studies addressed corticosteroid PK in relation to efficacy over a very short study period [57, 58]. In ten patients with sarcoidosis, the effect of a single dose of 75 mg prednisolone on the serum angiotensin-converting enzyme (ACE), a biomarker to monitor disease progress, was investigated [58]. No significant difference in serum ACE concentrations were observed within a 24-h study period, concluding that a corticosteroid treatment course of several weeks would have been more appropriate to study the effect on serum ACE. The same accounts for the study that failed to find a correlation between the systemic budesonide AUC and clinical response to therapy in patients with Crohn's disease over a 7-day follow-up period [57].

3.5 Associations Between Pharmacokinetics and Toxicity in Adult and Paediatric Patients

The relationship between corticosteroid PK and steroid-related toxicities was addressed in ten of the 12 studies [48, 50–54, 56–59]. There was some evidence considering a relationship between the PK of corticosteroids and toxicity. Patients with Cushingoid features or poor prednisolone tolerance had higher prednisolone AUC and AUC_{unb} compared with patients without these steroid-related side effects [48, 50]. Correlations between Cushing score and AUC, and between Cushing score and C_{max} were moderate ($r_s = 0.60$) and strong ($r_s = 0.72$), respectively [56]. Maintaining a prednisolone $AUC_{unb} < 324$ μg·h/L may minimise corticosteroid-related adverse events in patients requiring prolonged therapy [48].

Three studies observed correlations between prednisolone PK parameters and the occurrence of metabolic and cardiovascular adverse events [48, 50, 56]. At least one prednisolone-related adverse event was observed in 56% of 25 patients with lupus nephritis, with a significantly higher prednisolone AUC_{unb} in patients with Cushingoid features compared with patients without these features ($p = 0.019$) [48]. However, PK parameters did not differ between patients with infection, dyslipidaemia or hyperglycaemia compared with patients without these adverse events. Similarly, NS patients with poor prednisolone tolerance had a higher prednisolone AUC ($p < 0.05$) [50]. It was observed that 40% of paediatric patients with a prednisolone AUC above the threshold experienced Cushingoid appearances, growth retardation, bone demineralisation and necrosis, hypertension and cataract. In addition, a nearly twofold higher C_{max} and AUC were observed in patients with Cushingoid features compared with patients without these features [56]. Moderate and strong correlations were found between AUC and Cushing score ($r_s = 0.72$) and between C_{max} and Cushing score ($r_s = 0.78$), respectively. There was no significant correlation established between Cushing score with either cumulative steroid dose, disease activity or with cortisol.

In contrast with these findings, three studies did not find associations between prednisone/prednisolone dose or PK and adverse events [51, 53, 54]. In a recent, relatively large cohort of 104 children with NS, there were no differences in prednisolone AUC_{unb} between patients with Cushingoid features, alterations in behaviour, striae, severe infections and high blood pressure and patients without these steroid-related toxicities [54]. Moreover, time to first remission and frequency of relapses did not differ between patients with and without steroid-related toxicities. Interestingly, a steroid-dependent episode of NS was found to occur less frequently in patients who showed early signs of Cushingoid appearance, suggesting that both characteristics might result from increased sensitivity to prednisolone. Furthermore, in

17 patients with various underlying immune diseases, no correlations were found between the plasma protein binding parameters (k_{alb}, k_{CBG} and binding capacity for CBG to prednisolone) and adverse events of prednisone [51]. However, all five patients with Cushingoid features were SLE patients. Surprisingly, not even one severe steroid-related adverse event or case of drug intolerance was seen in 13 patients with NS on a 1 mg/kg/day prednisone treatment within the 6-month follow-up of the study [53].

In addition to these associations with clinical features of toxicity, a relationship between corticosteroid PK or dose and direct biochemical toxicity, cortisol suppression, has been observed in patients with Crohn's disease, sarcoidosis and RA [52, 57–59]. The unwanted systemic, PD action of oral budesonide in patients with Crohn's disease was reflected as decreased morning plasma cortisol levels after 1 week of budesonide 3 mg trice daily ($p < 0.01$) [59]. Although non-significant, patients with the highest budesonide AUC had the strongest plasma cortisol suppression, up to a plasma cortisol AUC decrease of 90% [57]. Reversible adrenal suppression was most pronounced in children < 12 years of age [59]. However, only a dose-related suppressive effect of budesonide was suggested. In addition, RA patients with a maintenance dose of ≥ 7.5 mg prednisolone for a mean of 10.3 years had fasting plasma cortisol concentrations of < 276 nmol/L with nihil response to prednisolone dose reduction [52]. This was unlike patients with ≤ 5 mg prednisolone who had cortisol > 276 nmol/L, in whom the gradual reduction of prednisolone increased plasma cortisol concentrations accordingly. This was suggested to be the result of HPA axis suppression, which is known to be related to the dose and duration of steroid therapy [52]. Even after a single dose of 75 mg prednisolone, the biological effect on cortisol suppression endures for at least 15 h [58].

4 Discussion

4.1 Variability in Corticosteroid Pharmacokinetics

A large IIV in corticosteroid PK among patients with immune and inflammatory diseases was described in almost all studies. This was in accordance with findings in other populations with an indication for corticosteroids [16, 17]. Also a large IIV in prednisolone f_{unb} was observed in patients receiving the same prednisone dose. This was mainly attributed to the non-linear protein binding of prednisolone in the therapeutic dosing range observed at doses > 20 mg [12].

Neither age, type of disease, nor disease state seemed to influence corticosteroid PK. However, this may be due to the small number of patients studied. In a relatively large cohort of 54 patients with severe asthma, a significant higher prednisolone clearance was seen in children < 12 years of age compared with older children and young adults (after BW correction) [20]. Regarding disease state, it seems plausible that the reduced capacity of binding sites to serum proteins, such as albumin during the active phase of diseases, might result in significant PK differences compared with healthy volunteers or patients who are in remission. This was observed in other studies [21–24].

4.2 Evidence on the Relationship Between Pharmacokinetics of Corticosteroids and Efficacy

Despite the widespread and decades-long use of corticosteroids for immune diseases, there is only limited and inconclusive data on the relationship between PK of corticosteroids and efficacy. Surprisingly, the findings of the few studies summarised in this review were not in agreement with the results in other diseases treated with corticosteroids [30, 31, 60]. In adult kidney transplant patients, a relationship between prednisolone AUC and kidney transplant rejection was observed [30]. Transplant patients with an acute rejection had a significant lower prednisolone AUC compared with patients without rejection. For methylprednisolone, a relationship between the PK parameters and kidney transplant rejection was observed as well [60]. Transplant patients without rejection had significantly higher AUC and C_{max} in contrast with patients with so called rejection episodes. In paediatric patients with ALL, a higher risk of relapse was associated with a lower dexamethasone AUC [31]. However, there were also some conflicting findings. Recently, Sassen et al. suggested no association between prednisolone PK and age, disease parameters or other treatment outcomes in paediatric ALL patients [61].

The study of Abd Rahman et al. in 25 adult patients with lupus nephritis, did not find differences in both prednisolone AUC and AUC_{unb} between responders and non-responders, despite that the study was scored with the highest level of evidence in this review (level 2) [48]. Nonetheless, this study has its caveats. Despite the still debatable sample size, it was stated by the authors that they may have failed to detect differences between PK and treatment response because of the complex and intracellular binding processes of corticosteroids and the fact that the study only examined drug exposure at one point in time. Therefore, they concluded that a prospective study is necessary to confirm their findings and to characterise further optimal drug exposure in different clinical settings.

Many of the other included studies (level 3–5) did not find associations between PK and disease parameters [52, 54, 57, 59]. A plausible explanation might be that this association between corticosteroid exposure and disease parameters is

relatively weak compared with inherent intra- and interpatient variability, possibly further complicated by the small sample sizes of the investigated cohorts or suboptimal study design. For example, participants in the study of De Silva et al. received a 10-mg study dose reduced at weekly intervals to eventually 5 mg, irrespective of the pre-trial maintenance prednisolone dose [52]. The pre-trial treatment dose and duration was mean 6.6 (range 4–12.5) mg prednisolone and mean 5.75 (range 1–20) years, respectively. Another example is the study of Teeninga et al., who applied an interesting, empirical approach by measuring prednisolone concentrations in saliva to estimate the unbound prednisolone concentration in serum [54]. To do so, they used a model previously developed in healthy adults and allometrically BW-scaled this to children. However, as the authors note, the strategy was based on the assumption that the relationship between the prednisolone concentration in saliva and serum in children is equal to that in healthy adults.

Regarding the convincing data of a PK/PD relationship in the organ transplant setting and the considerable room for improvement of treatment efficacy in immune diseases, such as in ulcerative colitis and graft versus host disease, there is a clear need to further investigate the potential PK/PD relationship of corticosteroids as a strategy to further improve treatment outcome [4–7].

4.3 Evidence on the Relationship Between Pharmacokinetics of Corticosteroids and Toxicity

There was some evidence for a relationship between the PK of prednisolone and (the severity of) Cushingoid features in both adult and paediatric patients [48, 50, 56]. There were also conflicting findings, since some studies did not find such association, despite a large cohort with 104 participants [53, 54].

We know that a potential exposure–toxicity relationship of corticosteroids exists, as such a relationship was already seen in transplant patients with low-dose prednisolone maintenance therapies [19, 41, 62]. Kidney transplant patients with Cushingoid features had a significant higher prednisolone AUC and AUC_{unb} compared with transplant patients without these features [19, 41]. Prednisolone AUC_{unb} was positively correlated with waist to upper arm circumference ratio, as a measure for fat distribution characterising Cushingoid appearance ($p < 0.05$) [62]. Moreover, Cushingoid transplant patients also had a significantly increased C_{max}, longer half-life and decreased clearance compared with patients without those Cushingoid features [41]. Concomitant therapy with cyclosporine A and oestrogens and female sex were prognostic factors in increased prednisolone AUC and development of steroid-related adverse events [19]. Therefore, a cut-off prednisolone AUC of 108 μg·h/L per milligram was suggested in the renal transplant setting, with a diagnostic sensitivity of 71% and 100%, a specificity of 57% and 67% and a predictive value of 45% and 87.5% for the development of toxicity in men and women, respectively. There are no specific reasons to assume that an exposure–toxicity relationship of corticosteroids in the transplant setting may be different in immune diseases. Therefore, the suggestion of Abd Rahman et al. to maintain a prednisolone $AUC_{unb} < 324$ μg·h/L to minimise corticosteroid-related adverse events in patients with an immune disease requiring prolonged therapy seems feasible as well [48]. However, we need to have a discerning eye and address that the lack of a significant association between corticosteroid exposure and toxicity parameters might also be explained by inherent variability that is affected by non-corticosteroid factors. Nonetheless, more consistent and sufficient studies derived from large and well-defined cohorts are needed to fully quantify the association between the PK of corticosteroids and toxicity, also performed in different immune diseases and addressing different steroid-related toxicities.

Of note, the suggested cut-off prednisolone AUC of Baron et al. seems debatable [50]. They found that paediatric patients with prednisolone AUC $< 3840 \times 10^4$ μg·h/L (originally noted as < 640 μg·min/mL in the article) all tolerated their treatment well compared with 40% of patients with a prednisolone AUC above 3840×10^4 μg·h/L. However, these AUCs seem not plausible compared with values for AUC found in other studies after either low or high doses of prednisolone. Therefore, the results of this study should be interpreted with caution.

Lastly, some studies did not investigate relations between PK parameters of the corticosteroids and (direct) toxicity, despite thorough PK analysis and the availability of adverse event data [49, 59].

4.4 Strengths, Limitations and Recommendations

This review gave an overview of the published studies that investigated PK/PD relationships of systemic corticosteroids in autoimmune and inflammatory diseases. It revealed many limitations of the included studies, as summarised below, and concluded that a proper investigation of the potential associations between the PK/PD relationship of corticosteroids in autoimmune diseases, considering both efficacy and toxicity outcomes, is highly needed.

A first limitation was that the total number of PK/PD studies of corticosteroids within the scope of this review was low, as well as the number of participants included in each study. Therefore, interpretation of non-significant results should be done with caution. It also becomes challenging to extrapolate results from a certain specific disease population to another with different dosing strategies and

potentially different corticosteroid sensitivity. Second, many different analytical techniques were used to measure cortisol and total and unbound prednisolone concentrations. A part of the included studies assessed associations with AUC and others with AUC_{unb}. The same accounts for the many different methods that were used to score toxicity. Lastly, every disease has its own standard regimen with concomitant medication potentially influencing clinical outcome, making it hard to differentiate between certain endpoints [48, 49, 57]. The same caveat is applicable for studies that included patients who used corticosteroids up to 20 years prior to the performed study, or did not mention any use of concomitant medication that could either influence corticosteroid PK or clinical outcome [48, 50–56].

We recommend prospective research to fully quantify the associations between the PK of corticosteroids and efficacy/toxicity outcomes. Cohorts should be large and well defined to be able to find significant associations. Patients should be newly diagnosed or relapsed, without a pre-trial maintenance corticosteroid dose. Follow-up should be at multiple moments over the course of weeks to months, dependent on the immune disease and outcome studied. For this, it should be taken in mind within what time a clinical effect or adverse event may be assumed to occur. For example, it is possible that (long-term) steroid toxicity will not be revealed when there is only one moment of follow-up some weeks after treatment initiation. In addition, steroid-related toxicity should be scored in a uniform way, using for instance the Glucocorticoid Toxicity Index [63]. Moreover, mental adverse effects are not frequently studied, while these complications may be an important influencing factor for a patient's quality of life. So far, there are no (comprehensive) validated questionnaires that can be used to assess mental adverse effects. Furthermore, associations should be made with the protein-unbound drug, because in general, the unbound plasma concentrations of pharmaceutical compounds exert the clinical effects and/or toxicities. In addition, in multiple studies, it was suggested that differences in corticosteroid PK were not a major determinant of drug response, but that unknown PD mechanisms or the heterogeneity in the pathogenesis of the disease might influence the efficacy of corticosteroids [50, 53, 55]. Therefore, the inflammatory profile of the disease should be taken into account as well. This should also include blood cell counts, such as T lymphocytes, in order to assess the relevant association between the grade of immune suppression and clinical outcome. Lastly, it was suggested that the high incidence of adverse events during chronic corticosteroid use and the frequency of therapeutic failures indicate that there is a need for pharmacological surveillance and therapeutic drug monitoring of plasma concentrations and protein binding, allowing more precise corticosteroid dosing [51, 56]. Therefore, the goal of future PK/PD research should be to optimise drug dosing for a specific disease type or population, or to develop a target window (threshold and/or cut-off) steroid $AUC_{(unb)}$ in order to optimise treatment efficacy and reduce toxicity.

5 Conclusion

This review aimed to give an overview of the currently published studies that investigated the PK/PD of systemic corticosteroids in autoimmune and inflammatory diseases. A large IIV of corticosteroid PK was described in all studies. There was only limited and insufficient evidence for a relationship between the PK of corticosteroids and efficacy, whereas there was some evidence for a relationship between the PK of corticosteroids and toxicity in both adult and paediatric patients.

Steroid-refractory disease as well as steroid-related toxicities remain major concerns with corticosteroid therapy, both with significant impact on the quality of life and therapy compliance. Since corticosteroids are still a widely used immunosuppressant with highly empirical dosing regimens, it is important to conduct prospective research on this potential relationship. As was already suggested in the 1980s, corticosteroids seem to have the potential for PK-based individual dosing strategies [51]. This way, optimalisation of the individual AUC to corticosteroids may decrease the incidence of adverse events while maintaining or even improving efficacy.

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