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Syndrome de Cushing iatrogène et situations à risques : revue systématique de la littérature

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Liste des abréviations

ACTH	Hormone Adrenocorticotrope
AIS	Anti-Inflammatoire Steroïdien
CRPV	Centre Régional de Pharmacovigilance
EI	Effets Indésirables
GC	Glucocorticoïdes
HPA	Hypothalamic-Pituitary-Adrenal
HCPC	Hierarchical Clustering on Principal Components
MeSH	Medical Subject Heading
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
SCI	Syndrome de Cushing d'origine Iatrogène
VIH	Virus de l'Immunodéficience Humaine

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Introduction

Les glucocorticoïdes (GC) représentent une part importante de l'arsenal thérapeutique en médecine humaine. Les GC de synthèse communément nommés "corticoïdes" font partie de la classe thérapeutique des anti-inflammatoires stéroïdiens. Ils dérivent de l'hormone naturelle, le cortisol, appelée aussi hydrocortisone, qui présente des propriétés glucocorticoïdes (en particulier anti-inflammatoires) et des propriétés minéralocorticoïdes (antidiurétiques, antinatriurétiques et kaliurétiques). Le développement de la famille pharmacologique des GC a permis de potentialiser leurs effets anti-inflammatoires et de minimiser leurs effets minéralocorticoïdes. Elle comprend aujourd'hui dérivés synthétiques qui se distinguent par leur puissance anti-inflammatoire, leur durée d'action variable et la persistance plus ou moins importante d'une action minéralocorticoïde. Appartenant à la classe des anti-inflammatoires stéroïdiens (AIS), les GC interviennent dans la prise en charge de nombreuses pathologies chroniques, telles que l'asthme ou la dermatite atopique. Il est également fréquent de les voir prescrits en traitement de courte durée dans certaines infections, comme les angines ou les otites par exemple, lorsqu'il y a une forte composante inflammatoire.
Si leur utilisation est très variée, il en va de même pour les voies d'administrations utilisées. L'action des GC pouvant être locale ou systémique, il existe une grande variété de formes galéniques : comprimés, solutions buvables, collyres, sprays nasaux, solutions auriculaires, inhalateurs, solutions pour nébulisation, solutions injectables, pommades et crème, shampooing... Peu de classes pharmacologiques disposent d'autant de modes d'utilisation.

Le cortisol, naturellement synthétisé au niveau de la zone fasciculée de la corticosurrénale, intervient dans de nombreux métabolismes expliquant la diversité des effets indésirables. Les GC sont donc responsables de nombreux effets indésirables (EI) notamment liés à une consommation trop importante de corticoïdes, et en particulier le Syndrome de Cushing d'origine Iatrogène (SCI). La recherche d'un effet anti-inflammatoire nécessite des doses de GC correspondant à une hypersécrétion de cortisol. Cependant, ces GC n'activent pas seulement les récepteurs glucocorticoïdes des lymphocytes, mais aussi ceux des cellules de la peau, des muscles, des os, du foie, pouvant être à l'origine de ce SCI. Le SCI est la conséquence de la prise au long cours de glucocorticoïdes ou de l'administration d'un traitement associant un glucocorticoïde et des médicaments modifiant la pharmacocinétique de celui-ci.

Le SCI associe à des degrés divers :

• une obésité facio-tronculaire ;

• une hyperlipidémie, qui contribuerait à long terme au développement de l'athérosclérose ;

• une hypokaliémie et une rétention hydrosodée (œdèmes, hypertension artérielle) ;

• une intolérance au glucose, d'où l'éventuelle révélation ou décompensation d'un diabète ;

• des manifestations cutanées : atrophie cutanée, fragilité de la peau et des capillaires (lésions purpuriques, ecchymoses), acné, hypertrichose, vergetures, folliculites, retard à la cicatrisation des plaies ;

• une myopathie des ceintures : atrophie, faiblesse musculaire prédominant à la racine des membres inférieurs ;

• une déperdition osseuse, essentiellement trabéculaire : ostéoporose, fractures de vertèbres, côtes, col fémoral ;

• des ostéonécroses épiphysaires, parfois bilatérales, voire multifocales, touchant avec prédilection les têtes fémorales chez l'adulte et les condyles fémoraux chez l'enfant ;

• un retard de croissance chez l'enfant ;

• une aménorrhée, une perte du désir sexuel.

Etant donné les conséquences cliniques du syndrome de Cushing associé à la corticothérapie, il est essentiel de mieux connaitre les situations à risque.

L'objectif de ce travail était ainsi de déterminer, à partir de la littérature existante, s'il existe des situations ou des profils de patients plus à risque de présenter un SCI lors d'un traitement par GC. Cela doit permettre d'éclairer les professionnels amenés à prendre en charge un patient sous GC et de renforcer la vigilance pour les patients les plus à risque. Les résultats de cette recherche sont présentés dans ce travail de thèse.

Méthode

Dans un premier temps, il a été décidé de procéder à une revue de la littérature à partir des bases de données PubMed et Embase. L'objectif fixé était alors de collecter un maximum de cas-patient. Pour cela, la méthode employée fût d'utiliser une combinaison de « Medical Subject Headings » (MeSH). Le MeSH systématiquement employé était « Cushing Syndrome ». Il a été utilisé en association à « Iatrogenic disease » (maladie iatrogénique) et « Adverse effect » (effet indésirable).
Lors de ces recherches, nous avons constatés que beaucoup de GC différents étaient cités. Plus surprenant, les trithérapies contre le Virus de l'Immunodefficience Humaine (VIH) étaient également très fréquemment mentionnées.
Nous avons donc choisi, pour compléter ces recherches, d'utiliser sur Pubmed une combinaison de « Cushing Syndrome » avec les MeSH de toutes les molécules ressorties dans nos premières recherches, y compris les inhibiteurs enzymatiques et les antirétroviraux (ARV).

Les critères d'exclusion étaient l'absence d'une des données suivantes : le sexe du patient, son âge, les molécules employées ainsi qu'une description des symptômes non exhaustive.

Afin d'évaluer la qualité des articles inclus, nous avons utilisé la méthodologie suggérée par Murad et al. Cette méthode propose un outil pour évaluer la qualité méthodologique d'un article cas-patient sur quatre domaines : « selection, ascertainment, causality et reporting ». Ces différents aspects de la qualité des articles sont évalués au travers de huit questions. Ces questions permettent de mesurer la quantité d'information et leur qualité pour chaque article, comme par exemple les notions de délais d'apparition et de résolution des symptômes. Nous avons adapté les questions au contexte du SCI. Les résultats ont été résumés dans la partie résultats de la thèse (tableau 1 et les résultats en détails dans l'annexe 1).

Enfin, nous avons procédé à l'analyse statistique de notre échantillon. Notre objectif était de trouver des profils récurrents dans nos cas patients. Au vu du large jeu de données dont nous disposions, l'analyse par cluster s'est imposée comme le meilleur choix.
D'un point de vue statistique, notre approche s'est articulée en deux étapes. La première a été de réaliser une étude descriptive classique via une approche tabulaire centrée variable. Chaque variable a été ainsi décrite indépendamment, en utilisant les paramètres de position et de dispersion usuels (moyenne et écart-type pour les variables numériques, fréquences et effectifs pour les

variables catégorielles). La deuxième étape a été de réaliser une analyse descriptive multivariée centrée patient, par le biais de la réalisation d'une factorielle sur données mixte puis d'une classification hierarchique ascendante. Cette approche permet de créer des groupes homogènes de patients (patients les plus similaire possible au sein des groupes), avec des groupes qui diffèrent les plus possibles (les groupes sont les plus hétérogènes possibles).

Résultats

Situations posing higher risk for Iatrogenic Cushing Syndrome: a Systematic Review and Cluster Analysis

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Key Points

Question: In what situations are patients at greater risk of developing iatrogenic Cushing syndrome (ICS)?

Findings: In this systematic review, 183 ICS cases were studied to identify recurrent situations. We detected three main profiles : young patients treated by topical corticoids, patients treated with glucocorticoid injections for rheumatologic disorders, and asthmatic patients taking inhaled corticoids while undergoing antiretroviral therapies.

Meaning: Clinicians should neither ignore nor underestimate the risk of ICS in these situations.

Abstract

Importance: Widely used, glucocorticoids nonetheless have many metabolic side effects impacting patient's quality of life, including iatrogenic Cushing syndrome, especially when used at high doses over a long period.

Objectives: To identify situations and factors associated with an increased risk of iatrogenic Cushing syndrome.

Evidence Review: We searched PubMed/MEDLINE up to November 2021, using the term "Cushing syndrome" in combination with "iatrogenic disease," "adverse effect," or the name of a glucocorticoid or enzyme inhibitor. A total of 211 articles were retrieved for full-text assessment.

Findings: We included 147 articles in our review, for a total of 183 cases. Data extracted from them included age, gender, symptoms, drug administered, route of administration, and time between start of glucocorticoid treatment and diagnosis of iatrogenic Cushing syndrome. We performed a clustering analysis, identifying three distinct clusters. The first (n = 95) consisted of younger patients with diverse dermatologic disorders, ranging from atopic dermatitis (9%) to diaper rash (21%), using topical glucocorticoids like clobetasol (43%) or betamethasone (21%). The second (n = 32) included patients with rheumatologic disorders (31%) or back pain (22%) who were treated with repeated injections of steroids, usually triamcinolone (91%). The third (n = 56) included patients suffering from asthma (93%), taking inhaled glucocorticoids like fluticasone (86%) and antiretroviral therapies boosted by ritonavir (80%).

Conclusions and Relevance: We advise caution when prescribing glucocorticoids in these situations. Regular monitoring of symptoms is recommended for the prevention or early detection of iatrogenic Cushing syndrome.

Introduction

Cushing syndrome (CS) usually designates a set of clinical signs related to excess of endogenous glucocorticoids (GCs). The most frequent signs are lipodystrophy, commonly resulting in a rounded face (moon face) and fat pads on the shoulders (buffalo hump); skin atrophy; purple striae; muscular atrophy; hypertrichosis; decreased bone density; and diabetes or decompensation of a preexisting diabetes.[1] Children can also present with stunted growth.[2] Diagnosis relies on laboratory test results—in particular, elevated serum or urinary cortisol levels.[3] ACTH levels also guide diagnosis of CS, which can result from ACTH-secreting tumors or primary adrenal tumors[4]
By analogy, iatrogenic Cushing Syndrome (ICS) refers to adverse metabolic effects induced by exogenous GCs. Though the clinical signs are the same, cortisol levels are low because the exogenous steroids responsible for symptoms also inhibit ACTH secretion and, consequently, production of endogenous cortisol.[5] Synthetic GCs offer therapeutic benefit in the treatment of various rheumatic, pulmonary, gastroenterological, and skin diseases, but their prescription requires caution, due to potential adverse effects. ICS is usually the consequence of prolonged high-dose GC therapy.[6]
The diagnosis of ICS is generally straightforward and may be considered in the context of long-term GC. While the ability of high-dose oral corticosteroids to induce ICS is widely known, clinicians may underestimate the potential systemic effects of GCs administered through other routes (e.g., inhaled, intra-articular, or dermal), despite their frequent clinical use. Concomitant medications can also inhibit GC metabolism, and this may increase GC toxicity.[7]
We conducted a systematic review of case reports and case series concerning ICS. The purpose of this study was to raise awareness of ICS features and describe factors associated with ICS, including drugs administered, routes of administration, and patient profiles.

Methods

Data sources, search strategy and data extraction

We performed a systematic review per PRISMA guidelines included multiple bibliographic databases (eg, PubMed/MEDLINE, Embase) spanning all dates of publication up to November 21, 2020.[8]Algorithm search was detailed in figure 1. Initial search used [Cushing syndrome] AND ([iatrogenic disease] OR [adverse effect]. A supplementary search was performed on Pubmed/MEDLINE, using [Cushing syndrome] AND [beclomethasone] OR [betamethasone] OR [budesonide] OR [clobetasol] OR [dexamethasone] OR [fluticasone] OR [hydrocortisone] OR

[methylprednisolone] OR [mometasone] OR [prednisolone] OR [prednisone] OR [triamcinolone] OR [atazanavir] OR [cobicistat] OR [darunavir] OR [emtricitabine] OR [fluconazole] OR [itraconazole] OR [lamivudine] OR [lopinavir] OR [posaconazole] OR [ritonavir] OR [tenofovir] OR [voriconazole]. In addition to this computerized search, we examined bibliographies.
Records were screened to solely retain those concerning diagnoses of ICS based on laboratory test results (such as serum cortisol levels) or strong clinical evidence.

Eligibility criteria

All case reports and cases series involving human subjects, and for which the full text was available, were eligible. The methodological quality of case reports and cases series was assessed using the tool proposed by Murad et al.[9] modified to adapt it to the analysis of toxicological exposures associated with ICS. The results of this modified tool have been summarized by summing the scores of the eight binary responses into an aggregate score (Table 1). Details of the scores are provided in Supplemental Material.

Statistics

Quantitative data are expressed as mean (± standard deviation) or median (25th-75th percentiles), as appropriate. Categorical data are expressed as absolute value (percentage). Missing body weight data were imputed using weighted predictive mean matching.[10] This method robustly minimizes misspecification of the imputation model, performs as well as theoretically superior methods used for missing covariate data, and may be preferred when data are missing for <50% of cases and these data are not missing not at random (MNAR).[11] To identify high-risk conditions for developing ICS, a patient-centered analytical approach[12] was adopted. Patient profiles were identified using factor analysis of mixed data (FAMD) and hierarchical clustering on principal components (HCPC).[13] Comparisons between clusters were performed using chi-square or Fisher's exact tests (for categorical variables), or one-way ANOVA and Kruskal-Wallis tests (for continuous variables), as appropriate. Statistical analyses were carried out using R software (version 3.6.2). *P*-values less than .05 were considered significant.

Results

A total of 7,339 articles, published between 1972 and 2020, were identified through the initial

search and a supplementary search. After exclusion by title or abstract, and elimination of duplicates, 211 articles were retained for full-text assessment. Of these, 64 were excluded due to insufficient data, leaving 147 (see Figure 1 for article selection process and Figure 2 for distribution of publication dates). Ultimately, 183 patients (84 males, 99 females; mean age: 30.29 [±23.54]) were included. Table 2 summarizes patient characteristics, and further details are provided in Supplemental Materials on included studies[14–160].

Data extracted included age, gender, corticoids and enzyme inhibitors administered, their routes of administration, time between beginning of corticoid use and ICS diagnosis, ICS-related clinical and laboratory findings, the course of the syndrome, and outcomes. Unreported data were considered unavailable.

Clinical presentation

Symptoms most frequently described were moon face (91.3%), weight gain (54.1%), obesity (53.6%) buffalo hump (38.3%), hypertension (36.3%), and muscular weakness (29.5%). Serum cortisol was measured and found low in 82.0% of the cases. Other diagnostic tests performed for some patients included serum ACTH (low for 45.9%), hypothalamic-pituitary-adrenal (HPA) axis stimulation (low response for 43.2%), and urinary cortisol (low for 18.0%). On average, ICS was diagnosed 9.0 months (range: 2 weeks to 30 years) after the start of treatment, and symptoms resolved 4.87 months after diagnosis.

Drugs inducing ICS

The primary GC indications were asthma (31.3%); cutaneous disorders, including diaper rash (11.2%), psoriasis (7.8%), and atopic dermatitis (5.6%); and rheumatologic disorders, including arthralgia (6.7%) and back pain (5.0%). GCs were usually administered cutaneously (31.2%) or inhaled (28.4%). GC was also administered through intra-articular (9.1%), intramuscular (3.4%), intralesional (3.4%), or epidural (3.4%) injections; orally (7.4%); and nasally (3.4%). For 7.4% of the cases, multiple routes of administration were employed, but these were analyzed separately.

The GCs most commonly used were fluticasone (26.8%) and triamcinolone (25.1%), followed by clobetasol (23.0%), betamethasone (12.0%), and dexamethasone (9.3%). More rarely, the administration of two non-GC steroids appear to have induced ICS: medroxyprogesterone (1.1%) and fluorometholone (0.5%). In 33.9% of cases, the enzyme inhibitor ritonavir was taken alongside GCs, mostly in combination with other antiretrovirals (ARVs), such as lopinavir and darunavir. Fluconazole and other azole antifungals were also reported.

ICS management and outcomes

In most cases, once the diagnosis was made, corticoids causing the ICS were stopped, gradually (19.8% of cases) or abruptly (59.5%). In 12.2% of the cases, the patient was switched to a less potent GC; in 2.3% of the cases, the GC was switched and then treatment was stopped. For 73.1% of the cases, symptoms completely resolved ; and in 20.5% of the cases, resolution was incomplete or ongoing at the time of writing. Supplemental hydrocortisone was administered to 45.6% of the patients.

Patient profiles

Three clusters of patients were identified, according to the elbow rule and the inertia criterion, in addition to the interpretability of any identifiable clusters (***Tables 1 and 2***).

Cluster 1 (*n* = 95 ; 52 females and 43 males ; mean age 17.31 [±22.20]**)** was mostly composed of young patients with dermatologic disorders (atopic dermatitis, 9%; psoriasis, 15%; and diaper rash, 21%). Many were administered the topical steroids clobetasol (43%) and betamethasone (21%). Patients were younger (mean age : 17.31) than those in other clusters. No ARVs were taken in this cluster, and only 1 patient (1%) was administered an azole antifungal. Hypertrichosis was a more common ICS symptom (41%) in this group.

Cluster 2 (*n* = 32 ; 21 females and 11 males ; mean age 43.50 [±13.41]**)** primarily included patients with back pain (22%) or rheumatic conditions (31%). Most were given triamcinolone (91%), usually by injection (intra-articular, 50%; epidural, 19%; or intramuscular, 16%). Half of the patients in this group received enzyme inhibitors, including medication containing ritonavir (53%).

Cluster 3 (*n* = 56 ; 26 females and 30 males ; mean age 43.97 [±17.20]**)** principally consisted of patients with asthma (93%) or respiratory problems who were taking ARVs, usually ritonavir (80% of cluster members), and other anti-HIV drugs. Patients were primarily treated with fluticasone (86%). Corticoids received were most often inhaled (82%) or administered through multiple routes (14%).

Discussion

Clinical presentation and management of ICS

The clinical picture of ICS is fairly consistent. The most important symptom observed is moon face, which is also seen in endogenous Cushing syndrome. Other signs of lipodystrophy—obesity (53.6%) and buffalo hump (38.3%)—were also frequent. Laboratory test results usually supported the diagnosis. In 82.0% of the cases, serum cortisol levels were low: most of the time, this was considered key to diagnosis. Other laboratory analyses performed included urinary cortisol, serum ACTH, and HPA axis stimulation tests. In the majority of cases, however, these additional tests merely corroborated a diagnosis already confirmed by low cortisol serum levels and clinical signs. The average length of time (9.0 months) between the start of treatment and diagnosis of ICS was quite long. In part, this may reflect initial failure of patients and clinicians to link symptoms to their GC treatment, thereby delaying diagnosis of ICS. Yet it may also indicate that the risk of ICS increases with cumulative exposure to GCs, and conversely, that GC doses should be tapered as soon as possible.

Many treatment strategies were described in the articles reviewed. To address the excess in exogenous corticoids, treatment was usually stopped, gradually or abruptly. In some other cases, patients were switched to less potent corticoids.[25,45,48,81,95,96,109,112,141,156,161] This was justified when corticoids were still needed to treat patients' conditions, such as severe asthma. In cases of switching, symptoms often diminished, but we cannot conclude that this was related to the switch. Sudden cessation of GC treatment can lead to severe cortisol deficiency in cases of strong HPA axis depression ; and hydrocortisone substitution was required in 45.6% of the cases.

ICS resolved in the majority of cases, but recovery was incomplete or ongoing in 20.5% of the them. There were 6 deaths among the patients included,[26,40,107,127,138,161] but these were attributed to underlying diseases rather than ICS.

Situations posing high risk for ICS

Synthetic GCs were developed to boost anti-inflammatory effects and limit mineralocorticoid-associated effects, and they vary in the extent to which these aims are achieved. The search for an anti-inflammatory effect requires doses that activate GC receptors not only in lymphocytes, but also in skin, muscle, bone, and liver cells, which can lead to metabolic effects, and thus ICS. Most symptoms are reversible once the treatment is tapered or discontinued. Due to inhibition of the HPA axis, later hydrocortisone supplementation may be necessary.[162] Our review turned up no

reported cases of ICS in patients with conditions usually requiring high doses of GCs, such as vasculitis or giant cell arteritis, or receiving corticoids to prevent transplant rejection. We believe this is because clinicians are already knowledgeable of the risk and management of ICS in these GC indications, and sometimes have to tolerate the onset of ICS in the absence of therapeutic alternatives, even though the development of new biotherapies now allows the development of low-dose steroid approaches.

We found a wide range of GCs linked to ICS, and none can be singled out as the main culprit. They were mostly inhaled or administered cutaneously, but intramuscular, intra-articular, and intralesional injections were also given. However, the ICS cases in our review were associated with three main categories of patients—those with asthma, skin diseases, and rheumatic conditions, respectively—suggesting that these clusters represent situations for which the risk of ICS is still underestimated by clinicians.

Cluster 1 mostly included children with dermatologic disorders receiving topical steroids, usually clobetasol or betamethasone. No patient in this group was given ARVs. Topical administration normally has a local effect, and only a limited systemic effect. Yet GC strength and treatment duration could be important factors in the development of ICS.[41] The relatively young age of these patients may also play a role: young children have thinner skin, making transcutaneous penetration more likely, especially if the skin is damaged.[163] Hypertrichosis was most often reported in this cluster, possibly because hirsutism in youth attracts more attention from observers, and because of the route of GC administration. 15 (15.8%) patients presented stunted growth, wich can be a preocupping feature among these patients.

Patients in Cluster 2 had rheumatologic disorders and received steroid injections—intra-articularly for half of the patients. The majority were administered triamcinolone, the GC most commonly injected. In most cases, more than one injection had been administered before developing ICS : the average time between treatment initiation and diagnosis was around 7 months. Systemic effects of injected corticoids should not be overlooked—for example, GC injection is known to be a risk factor for decompensation in diabetic patients,[164,165]—and repeated injections can lead to ICS. Half of the patients were using ARVs, which increased GC levels in the blood as well as the risk of ICS.

Most patients in Cluster 3 were asthmatic and taking inhaled corticoids. Among inhaled GCs, fluticasone was apparently most often responsible for ICS, possibly due to its longer half-life.[166] Enzyme inhibitors significantly increase ICS risk: 80% of patients in this group were receiving ritonavir-boosted ARV therapy. Inhaled GCs have only mild systemic effects if they are not "boosted" by concomitant administration of an enzyme inhibitor.[167] The apparently higher risk of

ICS when inhaled fluticasone is combined with antiretrovirals, especially ritonavir, should not be ignored.

Limitations

Not all occurrences of ICS are reported in the literature, but only those involving novel situations, causes, or symptoms. We suspect that this is why there were so few cases involving common oral GCs, such as prednisone and prednisolone. It also implies that there are other ICS risk factors our review could not identify. We nonetheless believe our analysis to be of value as it reveals clinical situations that practitioners did not expect to pose a risk of ICS, and therefore merit special caution. To ensure sufficiently significant results, we had to limit the types of data extracted to those most commonly available in articles. For example, to evaluate patient exposure to a corticoid, we had to select the length of time between start of treatment and ICS diagnosis, as this information was provided in 80% of the cases. While corticoid dosage and frequency of administration are of interest, too few articles recorded them.

Conclusions

Clinicians should exercise caution when prescribing GCs in the clinical situations we have described and consider the risk factors mentioned. In most of the cases reviewed, only local effects of GCs were expected and systemic effects were vastly underestimated, until the development of ICS symptoms. While GCs remain an important part of the therapeutic arsenal of every clinician, factors altering pharmacokinetics (e.g., topical use on thinner or damaged skin) and pharmacodynamics (e.g., administration of enzyme inhibitors) must always be taken into account.

Figures and Tables

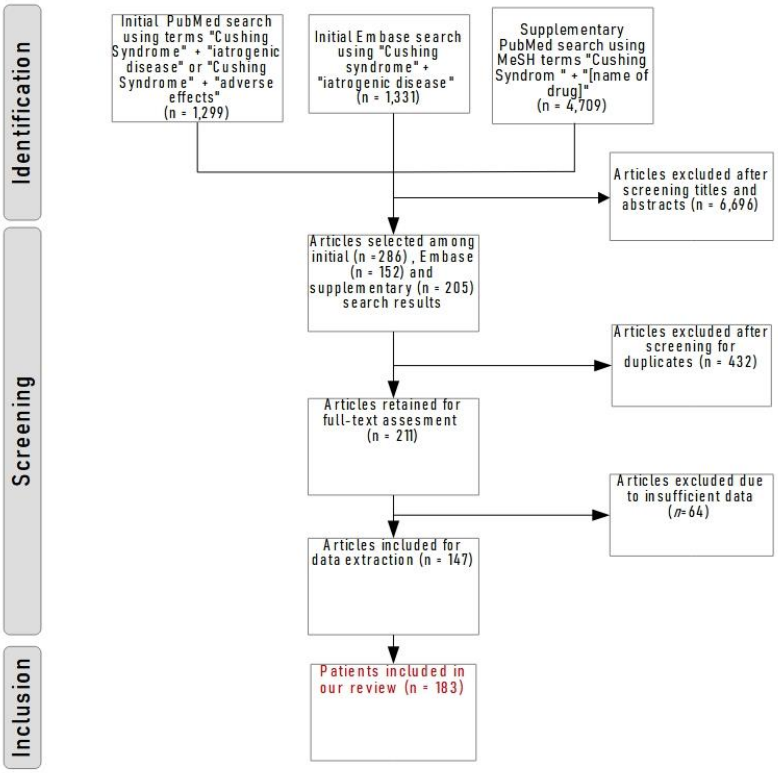

Figure 1. ***Flowchart for Case Inclusion***

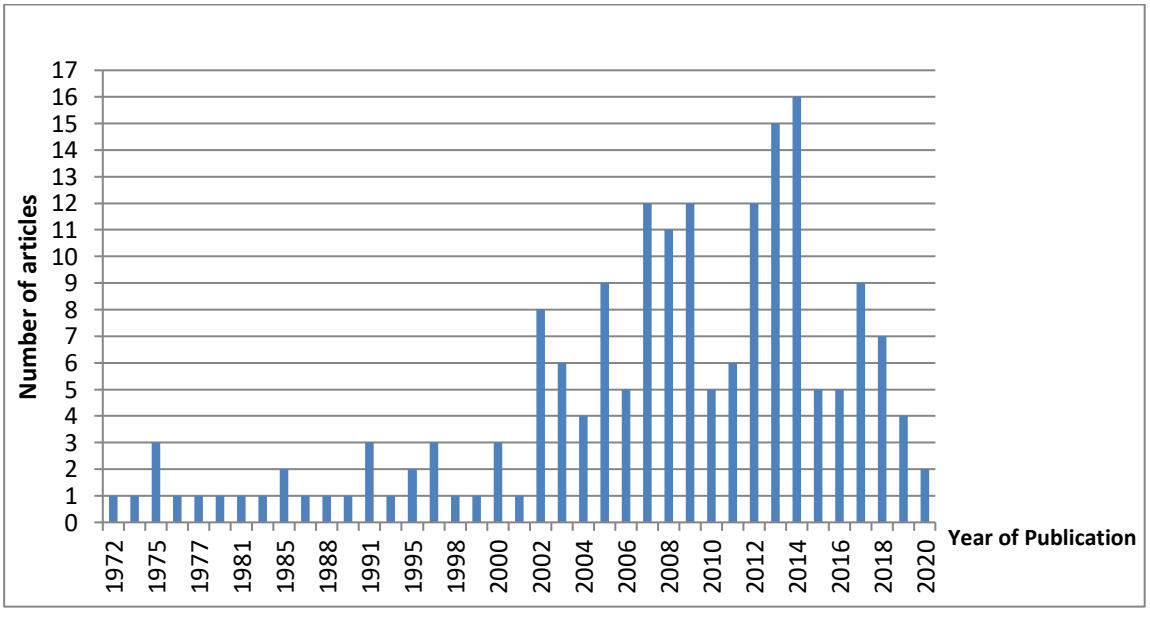

Figure 2. Distribution of ***Articles Included by Year of Publication***

Table 1. Results of the methodological quality assessment of cases report

Domains	Leading explanatory questions	Points	Results
Selection	1. Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported ?	1	0 (0)
Ascertainment	2. Was the exposure adequately ascertained ?	1	155 (84.7)
	3. Was the outcome adequately ascertained ?	1	121 (66.1)
Causality	4. Were all potential causal agents adequatly reported ?	1	183 (100)
	5. Were other alternative causes that may explain the observation ruled out ?	1	122 (66.7)
	6. Was the dechallenge phenomenon adequately reported ?	1	124 (67.8)
	7. Was follow up long enough for outcomes to occur ?	1	137 (74.9)
Reporting	8. Is the case described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice ?	1	156 (82.2)
	Overall score	**/10**	**6 (4 - 7)**

The overall score was calculated as a sum of points obtained at each item, median (interquartile range)

Table 2. Characteristics of Study Population and Clusters

Modality	Whole sample non imputed	Whole sample imputed (n=183)	Cluster 1 (n=95)	Cluster 2 (n= 32)	Cluster 3 (n=56)
Indication					
Asthma	56 (31.3)	56 (30.6)	4 (4.2)	0 (0.0)	52 (92.9)
Atopic Dermatitis	10 (5.6)	11 (6.0)	9 (9.5)	2 (6.2)	0 (0.0)
Back Pain	9 (5.0)	9 (4.9)	1 (1.1)	7 (21.9)	1 (1.8)
Diaper Rash	20 (11.2)	20 (10.9)	20 (21.1)	0 (0.0)	0 (0.0)
Lichen	5 (2.8)	5 (2.7)	5 (5.3)	0 (0.0)	0 (0.0)
Psoriasis	14 (7.8)	14 (7.7)	14 (14.7)	0 (0.0)	0 (0.0)
Rheumatic condition	12 (6.7)	13 (7.1)	3 (3.2)	10 (31.2)	0 (0.0)
Eye problems	8 (4.5)	8 (4.4)	5 (5.3)	2 (6.2)	1 (1.8)
Other	45 (25.1)	47 (25.7)	34 (35.8)	11 (34.4)	2 (3.6)
Drugs					
Fluticasone	49 (26.8)	49 (26.8)	1 (1.1)	0 (0.0)	48 (85.7)
Triamcinolone	46 (25.1)	46 (25.1)	15 (15.8)	29 (90.6)	2 (3.6)
Dexamethasone	17 (9.3)	17 (9.3)	14 (14.7)	2 (6.2)	1 (1.8)
Budesonide	10 (5.5)	10 (5.5)	1 (1.1)	0 (0.0)	9 (16.1)
Betamethasone	22 (12.0)	22 (12.0)	20 (21.1)	2 (6.2)	0 (0.0)
Clobetasol	42 (23.0)	42 (23.0)	41 (43.2)	0 (0.0)	1 (1.8)
Autre	23 (12.6)	23 (12.6)	14 (14.7)	2 (6.2)	7 (12.5)

Administration route					
Cutaneous	55 (31.2)	58 (31.7)	58 (61.1)	0 (0.0)	0 (0.0)
Epidural	6 (3.4)	6 (3.3)	0 (0.0)	6 (18.8)	0 (0.0)
Inhaled	50 (28.4)	52 (28.4)	6 (6.3)	0 (0.0)	46 (82.1)
Intra-articulary	16 (9.1)	17 (9.3)	1 (1.1)	16 (50.0)	0 (0.0)
Intra-muscular	6 (3.4)	6 (3.3)	1 (1.1)	5 (15.6)	0 (0.0)
Oral	13 (7.4)	13 (7.1)	12 (12.6)	0 (0.0)	1 (1.8)
Multiple Ways	13 (7.4)	13 (7.1)	4 (4.2)	1 (3.1)	8 (14.3)
Other	17 (9.7)	18 (9.8)	13 (13.7)	4 (12.5)	1 (1.8)
Enzymatic inhibitors					
Ritonavir	62 (33.9)	62 (33.9)	0 (0.0)	17 (53.1)	45 (80.4)
Lopinavir	21 (11.5)	21 (11.5)	0 (0.0)	2 (6.2)	19 (33.9)
Atazanavir	23 (12.6)	23 (12.6)	0 (0.0)	8 (25.0)	15 (26.8)
Lamivudine	18 (9.8)	18 (9.8)	0 (0.0)	3 (9.4)	15 (26.8)
Darunavir	8 (4.4)	8 (4.4)	0 (0.0)	2 (6.2)	6 (10.7)
Tenofovir	23 (12.6)	23 (12.6)	0 (0.0)	13 (40.6)	10 (17.9)
Emtricitabine	23 (12.6)	23 (12.6)	0 (0.0)	13 (40.6)	10 (17.9)
Zidovudine	9 (4.9)	9 (4.9)	0 (0.0)	1 (3.1)	8 (14.3)
Abacavir	6 (3.3)	6 (3.3)	0 (0.0)	0 (0.0)	6 (10.7)
Didanosine	7 (3.8)	7 (3.8)	0 (0.0)	1 (3.1)	6 (10.7)
Azole antifungal	9 (4.9)	9 (4.9)	1 (1.1)	0 (0.0)	8 (14.3)
Clarythromycin	2 (1.1)	2 (1.1)	0 (0.0)	0 (0.0)	2 (3.6)
Symptoms					
Moonface	167 (91.3)	167 (91.3)	89 (93.7)	29 (90.6)	49 (87.5)
Buffalo hump	70 (38.3)	70 (38.3)	36 (37.9)	16 (50.0)	18 (32.1)
Hypertrichosis	50 (27.3)	50 (27.3)	39 (41.1)	2 (6.2)	9 (16.1)
Striae	59 (32.2)	59 (32.2)	28 (29.5)	7 (21.9)	24 (42.9)
Ecchymosis	24 (13.1)	24 (13.1)	11 (11.6)	4 (12.5)	9 (16.1)
Obesity	98 (53.6)	98 (53.6)	53 (55.8)	15 (46.9)	30 (53.6)
Muscular atrophy	54 (29.5)	54 (29.5)	15 (15.8)	14 (43.8)	25 (44.6)
Skin thinning	21 (11.5)	21 (11.5)	10 (10.5)	3 (9.4)	8 (14.3)
Fatigue	29 (15.8)	29 (15.8)	4 (4.2)	10 (31.2)	15 (26.8)
Weight gain	99 (54.1)	99 (54.1)	51 (53.7)	11 (34.4)	37 (66.1)
Growth delay	15 (8.5)	15 (8.5)	15 (15.8)	0 (0.0)	0 (0.0)
Hypertension	66 (36.3)	66 (36.3)	35 (36.8)	13 (40.6)	18 (32.1)
Biological tests					
Low serum cortisol	150 (82.0)	150 (82.0)	72 (75.8)	27 (84.4)	51 (91.1)
Low urinary cortisol	33 (18.0)	33 (18.0)	12 (12.6)	6 (18.8)	15 (26.8)
Low serum ACTH	84 (45.9)	84 (45.9)	44 (46.3)	16 (50.0)	24 (42.9)
Low reaction to stimulation test	79 (43.2)	79 (43.2)	37 (38.9)	15 (46.9)	27 (48.2)

Discussion

Bien que nous disposions d'un système de pharmacovigilance opérationnel et actif en France, la notification des effets indésirables n'est pas systématique, en particulier quand les effets sont attendus et connus. Il est donc difficile de quantifier certains phénomènes iatrogènes par les seules déclarations d'EI aux Centres Régionaux de Pharmacovigilance (CRPV).
L'objectif de ce travail était de déterminer s'il existe des situations ou des profils de patients plus à risque de provoquer un SCI à partir d'une revue systématique de la littérature scientifique. L'approche analalytique en clustering sur un nombre conséquent de cas inclus a permis de regrouper des profils de patients récurrents. Trois profils de patients distincts ont donc pu être mis en évidence.

Le premier cluster nous a permis de mettre en valeur un risque de SCI chez les enfants traités par dermo-corticoïdes. Les effets systémiques d'un corticoïde par voie cutanée sont généralement limités. Plusieurs facteurs pourraient rentrer en jeu pour expliquer ce phénomène : l'âge des patients, la perméabilité acrrue de la barrière cutanée et la puissance des dermocorticoïdes utilisés. L'une des indications les plus fréquentes dans ce cluster était l'érythème fessier du nourrisson, et ainsi la peau lésée pourrait favoriser une absorption plus importante. Il apparait donc nécessaire d'être très prudent quant à l'usage de puissants dermo-corticoïdes chez les jeunes enfants. L'usage des GC par voie topique doit rester ponctuel et le plus court possible en population pédiatrique.

Le deuxième cluster montre un risque de SCI en cas d'utilisation de corticoïdes par voie injectable lors d'injections IM ou IA. Les méthodes et les sites d'injections étaient variables parmi les patients décrits dans la littérature, et notre étude ne retrouvait pas un surrisque de survenue de SCI selon le site d'injection. Près de la moitié des patients de ce cluster étaient traités par ARV, favorisant la survenue de SCI par interaction médicamenteuse avec le GC utilisé.

Enfin le troisième cluster était constitué de patients asthmatiques sous trithérapie contre le VIH. Les interactions médicamenteuses étaient fréquentes avec les ARV en raison de leur inhibition des cytochromes P450. Il est très probable que cette inhibition enzymatique soit à l'origine d'une baisse de l'élimination des corticoïdes inhalés, conduisant à un surdosage. La fluticasone était le GC le plus fréquemment rencontré dans ce cluster. L'utilisation d'autres médicaments sans GC

contre l'asthme (bêta-2 mimétiques d'action longue, anticholinergiques, etc.) pourrait être privilégiée en première intention. En cas d'utilisation de corticoïdes par voie inhalés, la dose efficace la plus basse devrait être recherchée.

Notre étude se basant sur la littérature scientifique, nous ne pouvons prétendre que ce sont les seuls profils à risque de SCI. Nous nous attendions notamment lorsque nous avons démarré ce travail à avoir un cluster de patients traités au long court par des corticoïdes par voie orale. Notre revue sytématique de la littérature n'a cependant pas retrouvé de tels cas. C'est pourtant un effet indésirable potentiel bien connu dans les traitements par GC oraux, et d'ailleurs largement notifié dans la base mondiale de pharmacovigilance. Cette discordance est liée à un biais de publication ; les publications scientifiques privilégiant davantage des cas cliniques originaux et des situations moins communes. Il serait donc intéressant de confronter ces résultats à la pratique dans les services de médecine interne et d'endocrinologie.

Cette étude, par une approche méthodologique innovante, a permis de mettre en lumière de nouvelles données via la littérature scientifique. L'exploitation des cas-patients de la littérature nous a permis de remettre l'accent sur le besoin d'une description la plus exhaustive possible des survenues de cas. Certaines données peuvent paraitre anodines pour un seul patient mais peuvent faire sens quand elles sont retrouvées dans d'autres cas-patients. Ces articles sont une source de données précieuse, et la qualité des études qui peuvent en découler, qu'il s'agisse de revues de la littérature ou de méta-analyses, dépend grandement de la précision avec laquelle les cas sont décrits.

Cette approche a permis de mettre en relief des situations moins évidentes dans la pratique courante. Il peut être intéressant de la voir appliquée à d'autres sujets, car bien que loin d'être applicable à tous les sujets, elle peut mettre en évidence des informations qui passeraient autrement inaperçues.

Conclusions

L'objectif de notre travail était de définir des profils à risque de SCI sur la base de la littérature scientifique. Grace à notre travail nous avons pu définir trois groupes de patients bien distincts et cohérents. Cela nous a permis d'établir des profils potentiels de patients à risque de développer un SCI.

Le premier profil est celui de jeunes patients traités par dermo-corticoïdes puissants, le deuxième profil est celui de patients présentant des problèmes de douleurs articulaires, traités par des injections de corticoïdes en IM ou en IA, et le dernier profil est celui des patients traités par corticoïdes inhalés pour leur asthme qui sont également sous traitement ARV. Cette méthode associant revue systématique de la littérature et clustering offre des résultats descriptifs bien ancrés dans une réalité clinique et favorise des messages de prévention et de bon usage.

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Annexe

Annexe 1 : Résultats du contrôle qualité

articles	Q. 1	Q. 2	Q. 3	Q. 4	Q. 5	Q. 6	Q. 7	Q. 8	**Scores**
Abma et al.	0	1	1	1	0	1	1	1	6
Agadi et al.	0	0	1	1	0	1	1	0	4
Al-Khenaizan et al.	0	1	1	1	0	1	1	1	6
Albert et al.	0	1	1	1	1	0	1	1	6
Atabek et al.	0	1	1	1	1	1	1	1	7
Azevedo et al.	0	1	1	1	0	1	1	1	6
Barillas et al.	0	0	1	1	0	0	1	1	4
Bas et al.	0	1	1	1	1	1	1	1	7
Basu et al. *#1*	0	0	0	1	0	1	0	1	3
Basu et al. *#2*	0	0	0	1	0	1	0	1	3
Bhumbra et al.	0	1	1	1	1	1	1	1	7
Bjoner et al.	0	1	0	1	1	1	0	0	4
Blondin et al. *#1*	0	1	1	1	0	1	1	1	6
Boonen et al.	0	1	0	1	1	0	1	1	5
Bouldouyre et al.	0	1	1	1	1	1	1	1	7
Bulus et al. *#1*	0	1	1	1	1	1	1	1	7
Bulus et al. *#2*	0	1	0	1	1	1	0	1	5
Bulus et al. *#3*	0	1	1	1	0	1	1	1	6
Burger et al.	0	1	0	1	1	1	1	1	6
Castanedo-Cazares et al.	0	1	0	1	0	1	0	0	3
Cayir et al.	0	1	0	1	1	1	0	1	5
Chan et al.	0	1	0	1	0	1	0	1	4
Chiang et al.	0	1	1	1	1	1	1	1	7
Ciccone et al.	0	1	1	1	1	1	1	1	7
Clevenbergh et al.	0	1	1	1	1	1	1	1	7
Collet-Gaudillat et al.	0	1	0	1	1	1	0	1	5
Colpitts et al.	0	1	1	1	1	1	1	1	7
Coureau et al.	0	1	0	1	0	1	0	0	3
De watcher et al. *#1*	0	1	0	1	1	1	1	1	6
De watcher et al. *#2*	0	1	1	1	1	1	1	1	7
Decani et al. *#1*	0	1	0	1	1	1	0	0	4
Decani et al. *#2*	0	1	0	1	1	0	0	0	3
Decani et al. *#4*	0	1	0	1	1	1	0	0	4
Demirsoy et al.	0	1	0	1	0	1	0	0	3
Dort et al. *#1*	0	1	1	1	1	0	1	1	6
Dort et al. *#2*	0	1	1	1	1	0	1	1	6
Duman et al.	0	1	0	1	0	0	1	0	3
Dupont et al. *#1*	0	1	1	1	1	1	1	1	7
Dupont et al. *#2*	0	1	1	1	1	1	1	1	7
Dutta et al.	0	1	1	1	1	1	1	1	7
Edmonds et al. *#1*	0	1	1	1	1	0	1	0	5
Edmonds et al. *#2*	0	0	1	1	1	0	1	1	5
Edmonds et al. *#3*	0	1	0	1	1	0	1	1	5

Eeftinck et al. *#1*	0	1	1	1	0	1	1	0	5
Eeftinck et al. *#2*	0	1	1	1	0	0	1	0	4
Ermis et al.	0	1	1	1	1	1	1	1	7
Espiard et al.	0	1	0	1	1	1	0	1	5
Fairris et al.	0	1	0	1	1	1	0	1	5
Fesler et al. *#2*	0	1	1	1	0	0	1	1	5
Finken et al.	0	1	1	1	1	0	1	1	6
Franke et al.	0	1	1	1	0	1	1	0	5
Frankel et al.	0	1	0	1	0	1	0	1	4
Frias et al.	0	1	1	1	1	1	1	1	7
Fukuhara et al.	0	1	1	1	1	1	1	1	7
Gen et al.	0	1	1	1	1	1	1	1	7
Gillani et al.	0	0	0	1	0	0	0	0	1
Gillett et al.	0	1	1	1	1	1	1	1	7
Gold-Von Simson et al.	0	1	0	1	1	1	0	1	5
Grierson et al.	0	1	1	1	1	0	1	1	6
Grubb et al.	0	1	1	1	1	0	1	1	6
Gupta et al.	0	1	1	1	1	1	1	1	7
Guven et al. *#1*	0	1	1	1	1	1	1	1	7
Guven et al. *#2*	0	1	0	1	1	1	0	1	5
Guven et al. *#3*	0	1	1	1	1	1	1	1	7
Guven et al. *#4*	0	1	1	1	1	1	1	1	7
Guven et al. *#5*	0	1	0	1	1	1	0	1	5
Hall et al.	0	0	1	1	0	0	1	1	4
Halverstam et al.	0	0	1	1	1	1	1	1	6
Hameed et al. *#1*	0	1	1	1	0	0	1	1	5
Hameed et al. *#2*	0	1	1	1	1	0	1	1	6
Hansen et al.	0	0	1	1	0	1	1	1	5
Hesse et al.	0	1	1	1	1	1	1	1	7
Ho et al.	0	1	1	1	1	1	1	1	7
Horani et al.	0	1	0	1	1	0	0	1	4
Iglesias et al.	0	1	1	1	1	0	1	1	6
Jakeman et al.	0	1	1	1	1	0	1	1	6
Jansen et al. *#1*	0	1	1	1	1	0	1	1	6
Jansen et al. *#2*	0	0	1	1	0	0	1	0	3
Jansen et al. *#3*	0	0	0	1	0	0	0	0	1
Jansen et al. *#4*	0	0	1	1	0	0	1	0	3
Jinagal et al.	0	0	1	1	1	1	1	1	6
Joe et al.	0	1	0	1	1	1	0	1	5
John et al.	0	1	1	1	1	1	1	1	7
Johnson et al. *#2*	0	1	1	1	1	1	1	1	7
Jolly et al.	0	1	1	1	1	1	1	1	7
Jones et al.	0	0	0	1	0	0	0	1	2
Joshi et al. *#1*	0	1	1	1	0	1	1	0	5
Karande et al.	0	1	1	1	1	1	1	1	7
Katar et al.	0	1	0	1	1	0	0	0	3
Kedem et al.	0	1	1	1	0	1	1	1	6
Kelly et al.	0	1	1	1	0	1	1	0	5
Kimmerle-Rolla et al.	0	1	0	1	1	1	0	1	5
Kong et al.	0	1	1	1	1	1	1	1	7

Kumar et al. *#1*	0	0	1	1	0	0	1	1	4
Kumar et al. *#2*	0	1	0	1	1	0	1	1	5
Lavin et al.	0	1	0	1	1	0	0	1	4
Lawlor et al.	0	1	1	1	1	1	1	1	7
Levine et al.	0	1	1	1	1	0	1	1	6
Liu et al.	0	0	1	1	1	0	1	1	5
Mahé et al. #1	0	0	1	1	0	1	1	1	5
Mahé et al. #2	0	0	1	1	0	1	1	0	4
Mahlab-Guri et al. *#1*	0	1	1	1	1	1	1	1	7
Mahlab-Guri et al. *#2*	0	1	1	1	1	1	1	1	7
Mahlab-Guri et al. *#3*	0	1	1	1	1	1	1	1	7
Main et al.	0	1	1	1	1	1	1	1	7
Marshall et al.	0	1	0	1	0	0	0	0	2
Maviki et al. *#1*	0	1	1	1	1	0	1	1	6
May et al.	0	1	0	1	0	1	0	0	3
McConkey et al.	0	1	1	1	1	0	1	1	6
Messina et al.	0	1	1	1	1	1	1	1	7
Monge et al.	0	1	0	1	1	1	0	1	5
Meikle et al.	0	1	1	1	1	0	1	1	6
Morales Conejo et al.	0	1	1	1	1	1	1	1	7
Narambu et al.	0	1	0	1	0	1	0	1	4
Nathan et al.	0	1	1	1	1	1	1	1	7
Negrini et al.	0	1	1	1	1	1	1	1	7
Nocent et al.	0	1	1	1	0	1	1	1	6
Notay et al.	0	0	1	1	0	1	1	1	5
Nutting et al.	0	1	0	1	0	1	0	1	4
O'Brien et al.	0	1	0	1	0	1	0	1	4
O'Sullivan et al.	0	1	0	1	0	1	0	1	4
Ohnishi et al.	0	1	1	1	1	1	1	1	7
Oluwayemi et al. *#1*	0	1	1	1	0	1	1	1	6
Oluwayemi et al. *#2*	0	1	1	1	0	1	1	1	6
Orton et al.	0	1	1	1	0	1	1	1	6
Ozdemir et al.	0	1	1	1	1	1	1	1	7
Ozerdem et al.	0	0	0	1	0	1	0	1	3
Özgüç Çömlek et al.	0	0	0	1	1	1	0	1	4
Pessanha et al.	0	1	1	1	0	0	1	1	5
Pilmis et al.	0	1	0	1	1	0	0	1	4
Pramick et al.	0	1	0	1	0	1	0	1	4
Quddusi et al.	0	1	0	1	1	0	0	1	4
Rainsbury et al.	0	1	1	1	0	1	1	1	6
Ramanathan et al.	0	1	0	1	1	0	1	1	5
Ritota et al. *#1*	0	0	1	1	0	0	1	0	3
Ritota et al. *#2*	0	0	1	1	0	0	1	0	3
Romano et al.	0	1	1	1	0	0	1	1	5
Rottenstreich et al.	0	1	1	1	0	1	1	1	6
Rouanet et al.	0	1	1	1	1	1	1	1	7
Rousseau et al.	0	1	0	1	1	1	0	1	5
Rustowka et al.	0	1	0	1	1	1	1	1	6
Sadao et al.	0	1	1	1	1	1	1	1	7
Sadarangani et al.	0	1	1	1	1	0	1	1	6

Salvatore et al.	0	1	0	1	1	0	1	1	5
Samaras et al. *#1*	0	1	0	1	0	1	1	1	5
Samaras et al. *#2*	0	0	1	1	1	1	1	1	6
Samaras et al. *#3*	0	1	0	1	0	1	1	1	5
Samaras et al. *#5*	0	1	0	1	1	1	0	0	4
Samaras et al. *#6*	0	1	1	1	0	1	1	1	6
Schwarze-Zander et al.	0	1	1	1	1	0	1	1	6
Schweitzer et al.	0	1	1	1	1	0	1	1	6
Semiz et al. *#1*	0	1	0	1	1	1	0	1	5
Semiz et al. *#2*	0	1	1	1	1	1	1	1	7
Seo et al.	0	1	1	1	1	1	1	1	7
Siklar et al.	0	1	0	1	1	0	0	1	4
Soldatos et al. *#2*	0	0	0	1	1	0	1	1	4
Song et al.	0	1	1	1	1	0	1	1	6
Spruyt et al. *#1*	0	1	1	1	1	1	1	1	7
St Clair et al.	0	1	1	1	1	0	1	1	6
St Germain et al.	0	1	1	1	1	1	1	1	7
Staughton et al. *#1*	0	1	1	1	1	1	1	1	7
Staughton et al. *#2*	0	1	1	1	1	1	1	1	7
Staughton et al. *#3*	0	1	1	1	1	1	1	1	7
Steven et al.	0	0	0	1	0	1	0	1	3
Teelucksingh et al.	0	1	1	1	1	0	1	1	6
Tempark et al.	0	1	1	1	1	1	1	1	7
Tsoukas et al.	0	1	1	1	1	1	1	1	7
Tuel et al.	0	1	0	1	0	0	1	1	4
Ustyol et al.	0	1	1	1	1	1	1	1	7
Valin et al. *#1*	0	1	1	1	0	1	1	1	6
Valin et al. *#2*	0	1	1	1	1	1	1	1	7
Valin et al. *#3*	0	1	0	1	1	1	1	1	6
Valin et al. *#4*	0	0	1	1	0	0	1	1	4
Valin et al. *#4bis*	0	1	1	1	1	1	1	1	7
Verma et al. *#1*	0	0	0	1	0	0	0	0	1
Vermeer et al.	0	1	0	1	1	1	1	1	6
Wilson et al.	0	1	1	1	1	1	1	1	7
Yoganathan et al.	0	1	0	1	1	1	1	1	6
Yombi et al. *#1*	0	1	1	1	1	0	1	1	6
Yombi et al. *#2*	0	1	1	1	1	0	1	1	6
Yombi et al. *#3*	0	1	1	1	1	0	1	1	6
Zil-E-Ali et al.	0	1	1	1	1	1	1	1	7
Zubillaga et al.	0	1	0	1	0	1	0	1	4

Annexe 2 : Caractéristiques détaillées de la population

articles	sex	age (years)	Corticoid	Administration route	Indication	ARV	Time to onset	Clinical symptoms	Laboratory tests	Therapeutic strategy	Outcome
Abma et al.	F	72	Clobetasol	Cutaneous	Psoriasis		3 years	Moon face, buffalo hump, striae, ecchymosis, Oedema, obesity, muscular atrophy	Low serum cortisol, low bone mineral density	Progressively stopped GC, cortisol supplementation was used	Complete recovery 2 years after diagnosis
Agadi et al.	F	0.25	Betamethasone	Unknown	Unknown		2.5 months	Moon face, striae, obesity, muscular atrophy, skin thinning		Progressively stopped GC	Complete recovery 1 month after diagnosis
Al-Khenaizan et al.	H	0.9	Clobetasol	Cutaneous	Diaper rash		7 months	Moon face, hypertrichosis, striae	Low serum cortisol	GC was switched to hydrocortisone	Complete recovery 2 months after diagnosis
Albert et al.	H	58	Triamcinolone	Epidural	Other motive	Ritonavir, Tenofovir, Emtricitabine	1 month	Moon face, buffalo hump, ecchymosis, oedema, obesity, hypertension	Low serum cortisol, low reaction to stimulation test	GC was already stopped at diagnosis	Complete recovery 1.5 month after diagnosis
Atabek et al.	F	0.75	Clobetasol	Cutaneous	Diaper rash		6 months	Moon face, buffalo hump, striae, obesity, weight gain, growth delay, hypertension	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Complete recovery 7 months after diagnosis
Azevedo et al.	M	39	Fluticasone	Inhaled	Asthma	Ritonavir, Atazanavir, Lamivudine	4 years	Moon face, buffalo hump, striae, oedema, obesity, muscular atrophy, skin thinning, hypertension	Low serum cortisol, low urinary cortisol, low serum ACTH, low bone mineral density	GC was switched to beclomethasone, cortisol supplementation was used	Complete recovery 7 months after diagnosis
Barillas et al.	F	2	Hydrocortisone	Oral	Other motive		1 year and 4 months	Moon face, hypertrichosis, weight gain		Unkown	Complete recovery, unknown delay
Bas et al.	M	0.33	Dexamethasone	Nasal	Other motive		4 months	Moon face, buffalo hump, growth delay	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Complete recovery 2 months after diagnosis
Basu et al. *#1*	M	7	Prednisolone	Oral	Other motive		4 months	Moon face, hypertrichosis, obesity		Directly stopped GC, cortisol supplementation was used	Unknown outcome
Basu et al. *#2*	M	1	Betamethasone	Oral	Other motive		6 months	Buffalo hump, hypertrichosis, obesity, hypertension		Progressively stopped GC	Unknown outcome
Bhumbra et al.	M	9	Fluticasone, Mometasone	Inhaled	Asthma	Ritonavir, Lopinavir, Lamivudine, Didanosine	2 months	Moon face, hypertrichosis, weight gain, hypertension	Low serum cortisol, low serum ACTH	Progressively stopped GC	Complete recovery 1.5 months after diagnosis
Bjoner et al.	M	NK	Dexamethasone	Oral	Back pain		9 months	Moon face, obesity, weight gain	Low serum cortisol, low serum ACTH	GC switched to prednisolone	Unknown outcome
Blondin et al. *#1*	M	71	Budesonide	Inhaled	Asthma		6 months	Moon face, buffalo hump, striae, ecchymosis, obesity, muscular atrophy, skin thinning, weight gain, hypertension	Low serum cortisol	Progressively stopped GC	Patient deceased

Boonen et al.	F	74	Triamcinolone	Intra-articular	Back pain		NK	Moon face, buffalo hump, obesity, muscular atrophy	Low serum cortisol, low urinary cortisol, low reaction to stimulation test	GC was already stopped at diagnosis	Partial recovery at time of publication
Bouldouyre et al.	F	43	Fluticasone	Inhaled	Asthma	Ritonavir, Atazanavir, Tenofovir, Emtricitabine	NK	Moon face, hypertrichosis, striae, obesity, muscular atrophy, weight gain, hypertension	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Complete recovery 6 months after diagnosis
Bulus et al. *#1*	M	0.25	Clobetasol	Cutaneous	Diaper rash		2 months	Moon face, hypertrichosis, weight gain	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Complete recovery 6 months after diagnosis
Bulus et al. *#2*	F	0.41	Clobetasol	Cutaneous	Diaper rash		1 month	Moon face, hypertrichosis, weight gain, growth delay	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Partial recovery at time of publication
Bulus et al. *#3*	F	3.5	Clobetasol	Cutaneous	Diaper rash		1 month	Moon face, weight gain	Low serum cortisol	Directly stopped GC	Complete recovery 2 months after diagnosis
Burger et al.	F	31	Prednisone, Fluticasone	Multiple routes	Asthma		11 months	Moon face, hypertrichosis, striae, ecchymosis, oedema, obesity, muscular atrophy, skin thinning, weight gain, hypertension	Low serum cortisol, low urinary cortisol, low serum ACTH	Directly stopped GC, cortisol supplementation was used	Partial recovery at time of publication
Castanedo-Cazares et al.	F	46	Betamethasone	Cutaneous	Atopic dermatitis		7 years	Moon face, buffalo hump, hypertrichosis, striae, obesity, weight gain, hypertension	Low serum cortisol	Directly stopped GC, cortisol supplementation was used	Unknown outcome
Cayir et al.	M	0.33	Clobetasol	Cutaneous	Diaper rash		1 month	Moon face, weight gain	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC	Partial recovery at time of publication
Chan et al.	F	72	Dexamethasone	Oral	Arthritis		1 year	Moon face, buffalo hump, obesity, muscular atrophy, skin thinning, hypertension	Low serum cortisol, glycemic disorder	Directly stopped GC, cortisol supplementation was used	Partial recovery at time of publication
Chiang et al.	M	18	Prednisolone, Dexamethasone, methylPrednisolone	Multiple routes	ocular troubles		8 months	Moon face, striae, obesity, weight gain,	Low serum cortisol, low urinary cortisol, low reaction to stimulation test	Progressively stopped GC, cortisol supplementation was used	Partial recovery at time of publication
Ciccone et al.	M	0.5	Betamethasone	Cutaneous	Atopic dermatitis		4 months	Moon face, hypertrichosis, obesity, hypertension	Low serum cortisol, low serum ACTH	Directly stopped GC, cortisol supplementation was used	Complete recovery 3 months after diagnosis
Clevenbergh et al.	M	33	Fluticasone	Inhaled	Asthma	Ritonavir, Lamivudine, Stavudine, Amprenavir	5 months	Moon face, weight gain	Low serum cortisol, low urinary cortisol, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Complete recovery 2 months after diagnosis

Collet-Gaudillat et al.	M	59	Fluticasone	Inhaled	Asthma	Ritonavir, Atazanavir, Lamivudine, Zidovudine	3 months	Moon face, striae, obesity	Low serum cortisol, low serum ACTH, low reaction to stimulation test, glycemic disorder	Directly stopped GC, cortisol supplementation was used	Partial recovery at time of publication
Colpitts et al.	F	47	Budesonide	Inhaled	Asthma	Ritonavir, Atazanavir, Emtricitabine, Raltegravir	6 months	Moon face, buffalo hump, muscular atrophy	Low serum cortisol, low serum ACTH	Directly stopped GC, cortisol supplementation was used	Complete recovery 7 months after diagnosis
Coureau et al.	M	0.91	Hydrocortisone, Betamethasone, Mometasone	Cutaneous	Atopic dermatitis		10 months	Growth delay, hypertension	Low serum cortisol	Directly stopped GC, cortisol supplementation was used	Complete recovery 4 months after diagnosis
De watcher et al. *#1*	M	0.33	Fluticasone, Budesonide	Multiple routes	Asthma		2 weeks	Moon face, obesity, weight gain, hypertension	Low serum cortisol, low serum ACTH	Progressively stopped GC, cortisol supplementation was used	Partial recovery at time of publication
De watcher et al. *#2*	F	NK	Budesonide	Inhaled	Asthma		6 weeks	Moon face, weight gain, hypertension	Low serum cortisol, low serum ACTH	Directly stopped GC, cortisol supplementation was used	Patient deceased
Decani et al. *#1*	F	58	Clobetasol	Cutaneous	Lichen		NK	Moon face, muscular atrophy, hypertension	Low serum cortisol, low serum ACTH	Progressively stopped GC	No recovery at time of publication
Decani et al. *#2*	F	51	Clobetasol	Cutaneous	Lichen		NK	Moon , hypertrichosis	Low serum cortisol, low serum ACTH	GC treatment was maintained	Unknown outcome
Decani et al. *#4*	F	55	Clobetasol	Cutaneous	Lichen		NK	Moon face, weight gain	Low serum cortisol, low serum ACTH	Progressively stopped GC	No recovery at time of publication
Demirsoy et al.	F	13	Clobetasol	Cutaneous	Psoriasis		5 years	Moon face, buffalo hump, striae, obesity	Low serum cortisol, low bone mineral density	Directly stopped GC, cortisol supplementation was used	Unknown outcome
Dort et al. *#1*	M	41	Triamcinolone	Epidural	Back pain	Ritonavir, Atazanavir, Tenofovir, Emtricitabine	3 months	Moon face, striae, obesity, hypertension	Low serum cortisol, low serum ACTH	GC was already stopped at diagnosis	Complete recovery 6 months after diagnosis
Dort et al. *#2*	F	4	Triamcinolone, Betamethasone	Intra-articular	Other motive	Ritonavir, Atazanavir, Tenofovir, Emtricitabine	NK	Obesity, muscular atrophy, hypertension	Low serum cortisol, low reaction to stimulation test	GC was already stopped at diagnosis, cortisol supplementation was used	Complete recovery 2 months after diagnosis
Duman et al.	F	61	Fluticasone, Mometasone	Multiple routes	Asthma		NK	Obesity, weight gain	Low serum cortisol	GC treatment was maintained	No recovery at time of publication
Dupont et al. *#1*	F	35	Fluticasone	Inhaled	Asthma	Ritonavir, Lopinavir, Tenofovir, Emtricitabine	1 month	Moon face, striae, obesity, muscular atrophy, weight gain	Low serum cortisol, low reaction to stimulation test	GC was switched to beclomethasone	Complete recovery 1.5 year after diagnosis
Dupont et al. *#2*	M	47	Fluticasone	Inhaled	Asthma	Ritonavir, Atazanavir, Tenofovir, Emtricitabine	2 months	Moon face, weight gain	Low serum cortisol low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Complete recovery 6 months after diagnosis

Dutta et al.	F	6	Dexamethasone	Nasal	Other motive		3 months	Moon face, hypertrichosis	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Complete recovery 1 month after diagnosis
Edmonds et al. *#1*	F	44	Triamcinolone	Intra-articular	Back pain		7 months	Moon face	Low serum cortisol low reaction to stimulation test	GC was already stopped at diagnosis	Complete recovery 1 month after diagnosis
Edmonds et al. *#2*	F	64	Triamcinolone	Intramuscular	Arthritis		3 months	Moon face, obesity, muscular atrophy, skin thinning, hypertension	low reaction to stimulation test	GC was already stopped at diagnosis	Complete recovery 6 months after diagnosis
Edmonds et al. *#3*	M	25	Methylprednisolone	Intra-articular	Arthritis		3 months	Moon face, striae, obesity	Low serum cortisol low reaction to stimulation test	GC was already stopped at diagnosis	Partial recovery at time of publication
Eeftinck et al. *#1*	M	26	Fluticasone	Inhaled	Asthma	Ritonavir, Atazanavir, Tenofovir, Emtricitabine	2 months	Moon face, weight gain	Low serum cortisol	GC was switched to beclomethasone	Complete recovery 3 months after diagnosis
Eeftinck et al. *#2*	M	32	Triamcinolone	Intra-articular	Unknown	Ritonavir, Atazanavir, Tenofovir, Emtricitabine	6 weeks	Moon face, weight gain, hypertension	Low serum cortisol	GC was already stopped at diagnosis	Complete recovery 1.5 month after diagnosis
Ermis et al.	M	0.33	Hydrocortisone, Clobetasol	Cutaneous	Diaper rash		2 months	Moon face, hypertrichosis, obesity, weight gain	Low serum cortisol, low urinary cortisol, low serum ACTH, low reaction to stimulation test	Progressively stopped GC	Complete recovery 2 months after diagnosis
Espiard et al.	F	62	Budesonide	Inhaled	Asthma		NK	Moon face, buffalo hump, obesity, muscular atrophy, skin thinning, hypertension	Low serum cortisol, low serum ACTH, glycemic disorder	Directly stopped GC, cortisol supplementation was used	Unknown outcome
Fairris et al.	F	55	Clobetasol	Cutaneous	Psoriasis		1 year	Moon face, buffalo hump, striae, skin thinning, hypertension	Low serum cortisol, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Unknown outcome
Fesler et al. *#2*	F	47	Fluticasone, Triamcinolone	Multiple routes	Back pain	Ritonavir, Lamivudine, Darunavir, Abacavir	1.5 months	Moon face, buffalo hump, striae, oedema, weight gain,hypertension	Low serum cortisol	GC was already stopped at diagnosis	Complete recovery, unknown delay
Finken et al.	F	6	Triamcinolone	Intralesional	Other motive		5 months	Moon face, obesity, weight gain, hypertension	Low serum cortisol, low urinary cortisol, low serum ACTH, low reaction to stimulation test	GC was already stopped at diagnosis	Complete recovery 10 months after diagnosis
Franke et al.	F	5	Dexamethasone	Cutaneous	Atopic dermatitis		NK	Moon face, hypertension	Low serum cortisol	Directly stopped GC, cortisol supplementation was used	Complete recovery 4 months after diagnosis
Frankel et al.	M	75	Budesonide	Oral	Other motive	Ritonavir, Atazanavir, Lamivudine, Nevirapine	2 weeks	Moon face, oedema, weight gain, hypertension	Low serum cortisol	Directly stopped GC	Unknown outcome

Frias et al.	M	41	Fluticasone	Inhaled	Asthma	Ritonavir, Atazanavir, Lamivudine, Tenofovir	7 months	Moon face, buffalo hump, striae, obesity, muscular atrophy, weight gain, growth delay	Low serum cortisol, low urinary cortisol, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Complete recovery 8 months after diagnosis
Fukuhara et al.	F	9	Betamethasone	Oral	ocular troubles		6 months	Moon face, buffalo hump, striae, obesity, weight gain, growth delay, hypertension	Low serum cortisol, low serum ACTH	Progressively stopped GC	Complete recovery 6 months after diagnosis
Gen et al.	F	48	Clobetasol	Cutaneous	Atopic dermatitis		10 months	Hypertrichosis, striae, obesity	Low serum cortisol, low urinary cortisol, low serum ACTH, low reaction to stimulation test, low bone mineral density, glycemic disorder	Directly stopped GC	Complete recovery 3 months after diagnosis
Gillani et al.	F	0.92	Fluticasone	Cutaneous	Diaper rash		2 months	Moon face, obesity, hypertension		Unknown	Unknown outcome
Gillett et al.	F	27	Fluticasone	Inhaled	Asthma	Ritonavir, Lopinavir, Saquinavir	NK	Buffalo hump, striae, obesity, muscular atrophy, weight gain	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Complete recovery, unknown delay
Gold-Von Simson et al.	M	16.9	Clobetasol	Cutaneous	Psoriasis		3 years	Moon face, buffalo hump, striae, obesity, weight gain, hypertension	Low serum cortisol, low urinary cortisol, low serum ACTH, low bone mineral density, glycemic disorder	Directly stopped GC, cortisol supplementation was used	Partial recovery at time of publication
Grierson et al.	F	47	Triamcinolone	Epidural	Back pain	Ritonavir, Atazanavir, Tenofovir, Emtricitabine	NK	Moon face, buffalo hump, striae, muscular atrophy	Low serum cortisol, low urinary cortisol, low serum ACTH, glycemic disorder	GC was already stopped at diagnosis, cortisol supplementation was used	Complete recovery, unknown delay
Grubb et al.	F	48	Triamcinolone	Intramuscular	Other motive		6 weeks	Moon face, buffalo hump, ecchymosis, muscular atrophy, hypertension	Low serum cortisol, low reaction to stimulation test	GC was already stopped at diagnosis	Complete recovery 4 months after diagnosis
Gupta et al.	M	45	Prednisone, Fluticasone	Multiple routes	Asthma	Ritonavir, Saquinavir, Efavirenz	5 months	Buffalo hump, striae, obesity, weight gain	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Progressively stopped GC	Complete recovery 8 months after diagnosis
Guven et al. *#1*	F	0.33	Clobetasol	Cutaneous	Diaper rash		1.5 months	Moon face, buffalo hump, obesity, hypertension	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Complete recovery 6 months after diagnosis
Guven et al. *#2*	F	0.25	Clobetasol	Cutaneous	Diaper rash		1.5 months	Moon face, buffalo hump, weight gain	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Partial recovery at time of publication
Guven et al. *#3*	M	0.58	Clobetasol	Cutaneous	Diaper rash		5 months	Moon face, buffalo hump, hypertrichosis, weight gain, hypertension	Low serum cortisol, low serum ACTH, low reaction to stimulation test	GC was switched to hydrocortisone	Complete recovery 2 months after diagnosis

Guven et al. *#4*	F	0.25	Clobetasol	Cutaneous	Diaper rash		2 months	Moon face, oedema, obesity, weight gain	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Patient deceased
Guven et al. *#5*	F	0.58	Clobetasol	Cutaneous	Diaper rash		3 months	Moon face, obesity, hypertension	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Unknown outcome
Hall et al.	F	53	Triamcinolone	Intra-articular	Other motive	Ritonavir, Darunavir, Raltegravir	1 month	Moon face, hypertension	glycemic disorder	GC was already stopped at diagnosis	Complete recovery 2 months after diagnosis
Halverstam et al.	M	11	Hydrocortisone	Cutaneous	Other motive		NK	Moon face, weight gain, obesity	low serum ACTH, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Complete recovery 4 months after diagnosis
Hameed et al. *#1*	M	13	Triamcinolone	Intra-articular	Arthritis		4 years	Moon face buffalo hump, striae, weight gain, growth delay, hypertension	Low serum cortisol	GC was already stopped at diagnosis	Complete recovery 8 months after diagnosis
Hameed et al. *#2*	F	3.6	Triamcinolone	Intralesional	Other motive		3 months	Moon face, hypertrichosis, hypertension	Low serum cortisol, low serum ACTH	GC was already stopped at diagnosis	Complete recovery 5 months after diagnosis
Hansen et al.	M	1.17	Betamethasone	Cutaneous	Atopic dermatitis		10 months	Moon face, hypertrichosis, weight gain, growth delay, hypertension		Directly stopped GC, cortisol supplementation was used	Complete recovery 1 year after diagnosis
Hesse et al.	F	25	Dexamethasone	Cutaneous	Other motive		NK	Moon face, buffalo hump , hypertrichosis, striae, obesity, muscular atrophy	Low serum cortisol, low urinary cortisol, low serum ACTH, glycemic disorder	Directly stopped GC	Complete recovery 7 months after diagnosis
Ho et al.	M	0.21	Clobetasol	Cutaneous	Diaper rash		2 months	Moon face, hypertrichosis, obesity, muscular atrophy, skin thinning, weight gain, growth delay, hypertension	Low serum cortisol, low urinary cortisol, low serum ACTH, glycemic disorder	Directly stopped GC, cortisol supplementation was used	Complete recovery 2 months after diagnosis
Horani et al.	M	21	Methylprednisolone	Epidural	Unknown		NK	Moon face, buffalo hump, striae, muscular atrophy, weight gain	Low serum cortisol, low urinary cortisol, low reaction to stimulation test	GC was already stopped at diagnosis	Unknown outcome
Iglesias et al.	F	45	Triamcinolone	Intramuscular	Other motive		4 months	Moon face, hypertrichosis, obesity, weight gain, hypertension	Low serum cortisol, low serum ACTH, low reaction to stimulation test	GC was already stopped at diagnosis	Complete recovery 4 months after diagnosis
Jakeman et al.	M	6	Triamcinolone	Intra-articular	Arthritis	Ritonavir, Atazanavir, Tenofovir, Emtricitabine	1 month	Moon face, hypertension	Low serum cortisol, low serum ACTH	GC was already stopped at diagnosis	Complete recovery 6 months after diagnosis
Jansen et al. *#1*	F	48	Triamcinolone	Unknown	Arthritis		NK	Moon face, buffalo hump	Low serum cortisol, low serum ACTH	GC was already stopped at diagnosis	Complete recovery 6 months after diagnosis

Jansen et al. *#2*	F	42	Triamcinolone	Intramuscular	Other motive		2 weeks	Moon face, weight gain		GC was already stopped at diagnosis	Complete recovery 3 months after diagnosis
Jansen et al. *#3*	F	28	Triamcinolone	Unknown	Other motive		2 weeks	Moon face, buffalo hump, weight gain		GC was already stopped at diagnosis	Unknown outcome
Jansen et al. *#4*	F	19	Triamcinolone	Unknown	Other motive		7 weeks	Moon face, buffalo hump, weight gain		GC was already stopped at diagnosis	Complete recovery 6 months after diagnosis
Jinagal et al.	M	NK	Betamethasone	Cutaneous	Other motive		6 weeks	Moon face, buffalo hump, obesity, weight gain	low serum ACTH	Progressively stopped GC	Complete recovery 3 months after diagnosis
Joe et al.	M	11	Betamethasone	Cutaneous	Psoriasis		NK	Moon face, buffalo hump, striae, obesity, weight gain	Low serum cortisol, low reaction to stimulation test	Directly stopped GC	Partial recovery at time of publication
John et al.	M	51	Fluticasone, Triamcinolone	Multiple routes	Other motive	Ritonavir, Atazanavir, Didanosine, Etravirine	NK	Moon face, buffalo hump	Low serum cortisol, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Complete recovery 1 year after diagnosis
Johnson et al. *#2*	F	15	Prednisone, Fluticasone	Multiple routes	Asthma	Ritonavir, Lopinavir, Lamivudine, Abacavir	NK	Moon face, hypertrichosis, striae, obesity, weight gain	Low serum cortisol, low serum ACTH	GC doses were lowered	Complete recovery 2.5 months after diagnosis
Jolly et al.	M	55	Fluticasone, Budesonide	Inhaled	Asthma	Ritonavir, Darunavir, Raltegravir, Maraviroc	NK	Moon face, striae, obesity, weight gain	Low serum cortisol, low urinary cortisol, low serum ACTH	GC was switched to beclomethasone, cortisol supplementation was used	Complete recovery 3 months after diagnosis
Jones et al.	F	48	Budesonide	Oral	Asthma		7 weeks	Moon face, buffalo hump, oedema, weight gain, hypertension		GC treatment was maintained	Partial recovery at time of publication
Joshi et al. *#1*	M	0.25	Dexamethasone	Nasal	Other motive		7 weeks	Moon face	Low serum cortisol	Progressively stopped GC	Complete recovery, unknown delay
Karande et al.	M	0.33	Betamethasone	Oral	Other motive		3 months	Moon face, obesity, hypertension	Low serum cortisol, low serum ACTH	Progressively stopped GC	Complete recovery 1 month and 3 weeks after diagnosis
Katar et al.	M	0.5	Clobetasol	Cutaneous	Other motive		3 months	Moon face, striae, obesity, muscular atrophy, weight gain, hypertension	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Unknown	Unknown outcome
Kedem et al.	F	37	Fluticasone	Inhaled	Asthma	Ritonavir, Lopinavir, Tenofovir, Emtricitabine	11 months	Striae, oedema, weight gain, hypertension	Low serum cortisol, low urinary cortisol	Directly stopped GC	Complete recovery 2 months after diagnosis
Kelly et al.	F	42	Clobetasol	Cutaneous	Psoriasis		2 years	Moon face ecchymosis, oedema, muscular atrophy, hypertension	Low serum cortisol, low urinary cortisol	Directly stopped GC	Complete recovery, unknown delay

Kimmerle-Rolla et al.	F	6	Dexamethasone	Nasal	Unknown		2 years	Moon face, buffalo hump, hypertrichosis, ecchymosis, obesity, weight gain	Low serum cortisol, low serum ACTH	Directly stopped GC, cortisol supplementation was used	Unknown outcome
Kong et al.	F	6	Medroxyprogesterone	Unknown	Other motive		NK	Moon face, buffalo hump, hypertrichosis, ecchymosis, obesity, muscular atrophy, weight gain	low urinary cortisol, low serum ACTH, low reaction to stimulation test, low bone mineral density	Directly stopped GC	Complete recovery, unknown delay
Kumar et al. *#1*	F	9	Triamcinolone	Intra-articular	Arthritis		NK	Moon face, buffalo hump, striae, muscular atrophy, weight gain		GC was already stopped at diagnosis	Complete recovery, unknown delay
Kumar et al. *#2*	F	7	Triamcinolone	Intralesional	Other motive		NK	Moon face, hypertrichosis, striae, weight gain	Low serum cortisol, low serum ACTH	GC was already stopped at diagnosis	No recovery at time of publication
Lavin et al.	F	39	Triamcinolone	Intracranial	Other motive		3 months	Moon face, buffalo hump, oedema, obesity, muscular atrophy, hypertension	Low serum cortisol, low urinary cortisol, low serum ACTH, low reaction to stimulation test	GC was already stopped at diagnosis	Partial recovery at time of publication
Lawlor et al.	M	34	Clobetasol	Cutaneous	Psoriasis		60 months	Moon face, striae, ecchymosis, obesity, skin thinning	Low serum cortisol, low reaction to stimulation test	Directly stopped GC	Complete recovery 8 months after diagnosis
Levine et al.	F	41	Triamcinolone	Intramuscular	Other motive		3 months	Moon face, hypertrichosis, weight gain	Low serum cortisol, low serum ACTH	GC was already stopped at diagnosis	Complete recovery 3 months after diagnosis
Liu et al.	F	25	Triamcinolone	Intralesional	Other motive		6 months	Moon face, hypertrichosis, striae, weight gain	low reaction to stimulation test	GC was already stopped at diagnosis	Complete recovery 6 months after diagnosis
Mahé et al. #1	M	9	Clobetasol	Cutaneous	Psoriasis		2 months	Moon face, buffalo hump		Directly stopped GC	Complete recovery 2 months after diagnosis
Mahé et al. #2	M	7	Clobetasol	Cutaneous	Psoriasis		3 months	Moon face, buffalo hump		GC was switched to betamethasone	Complete recovery, unknown delay
Mahlab-Guri et al. *#1*	F	12	Fluticasone	Inhaled	Asthma	Ritonavir, Lopinavir, Lamivudine, Zidovudine	6 months	Moon face, weight gain	Low serum cortisol, low urinary cortisol, low serum ACTH, low reaction to stimulation test	Progressively stopped GC	Complete recovery, unknown delay
Mahlab-Guri et al. *#2*	F	55	Fluticasone	Inhaled	Asthma	Ritonavir, Lopinavir, Lamivudine, Zidovudine	3 weeks	Moon face, weight gain	Low serum cortisol, low reaction to stimulation test	GC was switched to budesonide	Complete recovery 3 months after diagnosis
Mahlab-Guri et al. *#3*	F	65	Fluticasone	Inhaled	Asthma	Ritonavir, Lopinavir, Lamivudine, Zidovudine	NK	Moon face, weight gain	Low serum cortisol, low reaction to stimulation test	Progressively stopped GC	Complete recovery, unknown delay

Main et al.	F	2	Budesonide	Inhaled	Asthma		NK	Moon face, hypertrichosis, striae, weight gain	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Complete recovery, unknown delay
Marshall et al.	M	59	Fluticasone	Inhaled	Asthma	Ritonavir, Dasabuvir, Ombitasvir, Paritaprevir	NK	Moon face, buffalo hump, ecchymosis, oedema, obesity, muscular atrophy, skin thinning	Low serum cortisol, low urinary cortisol	Unknown	Unknown outcome
Maviki et al. *#1*	F	39	Triamcinolone	Unknown	Back pain	Ritonavir, Darunavir, Tenofovir, Emtricitabine	5 weeks	Moon face	low urinary cortisol, low reaction to stimulation test	GC was already stopped at diagnosis	Complete recovery, unknown delay
May et al.	F	49	Triamcinolone	Cutaneous	Other motive		NK	Moon face, buffalo hump, obesity, muscular atrophy, weight gain, hypertension	Low serum cortisol	Directly stopped GC, cortisol supplementation was used	Unknown outcome
McConkey et al.	F	39	Triamcinolone	Intraocular	ocular troubles	Ritonavir, Lopinavir, Tenofovir, Emtricitabine	1 month	Moon face, buffalo hump	Low serum cortisol, low serum ACTH	GC was already stopped at diagnosis	Complete recovery 1 month after diagnosis
Messina et al.	M	7.6	Dexamethasone, Betamethasone	Multiple routes	ocular troubles		6 months	Moon face, buffalo hump, hypertrichosis, obesity, weight gain, hypertension	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Complete recovery 4 months after diagnosis
Monge et al.	M	49	Fluticasone	Inhaled	Asthma	Cobicistat, Darunavir, Tenofovir, Emtricitabine	5 months	Moon face, buffalo hump, striae, oedema, obesity, muscular atrophy, weight gain	Low serum cortisol, low urinary cortisol, low serum ACTH, low bone mineral density	Progressively stopped GC, cortisol supplementation was used	Unknown outcome
Meikle et al.	F	51	Dexamethasone, Betamethasone	Ocular	ocular troubles	Ritonavir, Atazanavir, Tenofovir, Emtricitabine	8 months	Buffalo hump, weight gain	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Unknown	Complete recovery 1 year after diagnosis
Morales Conejo et al.	H	54	Fluticasone	Inhaled	Asthma	Ritonavir, Lopinavir, Lamivudine, Zidovudine	5 months	Moon face, buffalo hump, striae, obesity	Low serum cortisol, low serum ACTH	Progressively stopped GC	Complete recovery 6 months after diagnosis
Narambu et al.	H	0.42	Betamethasone	Oral	Other motive		4 months	Moon face, buffalo hump, obesity skin thinning, weight gain, growth delay	Low serum cortisol	Progressively stopped GC, cortisol supplementation was used	Unknown outcome
Nathan et al.	F	6	Betamethasone, Clobetasol	Cutaneous	Other motive		NK	Moon face, hypertrichosis, striae, ecchymosis, oedema, obesity, muscular atrophy, skin thinning	Low serum cortisol, low serum ACTH, glycemic disorder	Directly stopped GC, cortisol supplementation was used	Patient deceased

Negrini et al.	F	26	Clobetasol	Cutaneous	Psoriasis		2 years	Moon face, buffalo hump, striae, ecchymosis, obesity, weight gain, hypertension	Low serum cortisol, low urinary cortisol, low serum ACTH, low reaction to stimulation test, low bone mineral density	Directly stopped GC, cortisol supplementation was used	Complete recovery, unknown delay
Nocent et al.	H	38	Fluticasone, beclomethasone	Inhaled	Asthma	Ritonavir, Lopinavir, Lamivudine, Stavudine	NK	Moon face	Low serum cortisol	GC was switched to beclomethasone	Complete recovery 3 weeks after diagnosis
Notay et al.	F	6	Clobetasol	Cutaneous	Lichen		2 months	Moon face, weight gain		GC was switched to triamcinolone, and then stopped	Complete recovery 1 month after diagnosis
Nutting et al.	F	28	Betamethasone	Inhaled	Asthma		1 year	Moon face, striae, weight gain	Low serum cortisol, low urinary cortisol	Progressively stopped GC	Partial recovery at time of publication
O'Brien et al.	M	12	Prednisone	Oral	Atopic dermatitis		NK	Moon face, buffalo hump, hypertrichosis, striae, obesity	Low serum cortisol	GC was switched to hydrocortisone, and then stopped	Unknown outcome
O'Sullivan et al.	M	59	Triamcinolone	Intra-articular	Arthritis		8 years	Buffalo hump, ecchymosis, obesity, muscular atrophy, skin thinning	Low serum cortisol	Directly stopped GC, cortisol supplementation was used	Unknown outcome
Ohnishi et al.	M	31	Clobetasol	Cutaneous	Psoriasis		6 years	Moon face, striae, obesity, hypertension	Low serum cortisol, low serum ACTH	Directly stopped GC	Complete recovery 4 months after diagnosis
Oluwayemi et al. *#1*	M	1.58	Betamethasone	Inhaled	Other motive		3 months	Moon face, hypertrichosis, obesity, weight gain	Low serum cortisol	Progressively stopped GC	Complete recovery, unknown delay
Oluwayemi et al. *#2*	M	0.75	Betamethasone	Inhaled	Other motive		2 months	Moon face, obesity, weight gain, growth delay	Low serum cortisol	Directly stopped GC, cortisol supplementation was used	Complete recovery, unknown delay
Orton et al.	M	0.33	Dexamethasone	Inhaled	Other motive		6 weeks	Moon face, growth delay	Low serum cortisol	Progressively stopped GC	Complete recovery 2.5 months after diagnosis
Ozdemir et al.	M	0.58	Clobetasol	Cutaneous	Diaper rash		4 months	Moon face, buffalo hump, hypertrichosis	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Complete recovery 6 months after diagnosis
Ozerdem et al.	M	11	Prednisolone	Cutaneous	ocular troubles		6 months	Moon face, buffalo hump, hypertrichosis		Directly stopped GC	Unknown outcome
Özgüç Çömlek et al.	F	0.21	Clobetasol	Cutaneous	Diaper rash		2 months	Moon face hypertrichosis, obesity, weight gain	low serum ACTH	Directly stopped GC	Partial recovery at time of publication
Pessanha et al.	F	16	Fluticasone	Inhaled	Asthma	Ritonavir, Lamivudine, Stavudine	3 months	Moon face, striae, weight gain	Low serum cortisol, low urinary cortisol	GC treatment was maintained	Complete recovery 5 months after diagnosis

Pilmis et al.	F	51	Fluticasone	Inhaled	Asthma		1 year	Moon face, skin thinning, weight gain	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Unknown	Unknown outcome
Pramick et al.	F	7	Clobetasol	Cutaneous	Lichen		1 year and 6 months	Hypertrichosis, ecchymosis, obesity	Low serum cortisol	Directly stopped GC	Partial recovery at time of publication
Quddusi et al.	M	61	Betamethasone	Oral	Asthma		30 years	Ecchymosis, oedema, obesity, skin thinning	low urinary cortisol, low serum ACTH, low reaction to stimulation test, glycemic disorder	Unknown	Unknown outcome
Rainsbury et al.	M	15	Dexamethasone	Ocular	ocular troubles	Ritonavir, Lamivudine, Darunavir, Zidovudine	2 weeks	Moon face, weight gain, hypertension	Low serum cortisol	Progressively stopped GC	Complete recovery 3 months after diagnosis
Ramanathan et al.	M	35	Triamcinolone	Epidural	Back pain	Ritonavir, Tenofovir, Emtricitabine	1 month	Moon face, buffalo hump, weight gain, hypertension	Low serum cortisol, low serum ACTH, glycemic disorder	GC was already stopped at diagnosis	Partial recovery at time of publication
Ritota et al. *#1*	M	1	Triamcinolone	Intralesional	Other motive		5 weeks	Moon face, weight gain		GC was already stopped at diagnosis	Complete recovery 2 months after diagnosis
Ritota et al. *#2*	F	1.75	Triamcinolone, Dexamethasone	Multiple routes	Other motive		3 weeks	Moon face, hypertrichosis, weight gain		GC was already stopped at diagnosis	Complete recovery 1 year after diagnosis
Romano et al.	F	0.92	Triamcinolone, Dexamethasone	Multiple routes	ocular troubles		2 weeks	Moon face, hypertrichosis	Low serum cortisol, low serum ACTH, low bone mineral density	GC was already stopped at diagnosis	Patient deceased
Rottenstreich et al.	M	0.58	Dexamethasone	Nasal	Other motive		2 months	Moon face, hypertrichosis, obesity, weight gain, hypertension	Low serum cortisol	GC was switched to hydrocortisone, and then stopped	Complete recovery 1 month after diagnosis
Rouanet et al.	M	44	Fluticasone	Inhaled	Asthma	Ritonavir, Lopinavir, Abacavir, Didanosine	2 months	Moon face, striae, obesity, weight gain	Low serum cortisol, low reaction to stimulation test	Directly stopped GC	Complete recovery 1 month after diagnosis
Rousseau et al.	F	4	Fluticasone	Inhaled	Asthma	Ritonavir, Lopinavir, Tenofovir, Emtricitabine	10 months	Moon face, hypertrichosis, striae, ecchymosis, obesity, muscular atrophy, weight gain	Low serum cortisol, low urinary cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Unknown outcome
Rustowka et al.	F	4	Mometasone	Cutaneous	Atopic dermatitis		NK	Moon face, buffalo hump, hypertrichosis, obesity, muscular atrophy, skin thinning, weight gain, growth delay, hypertension	Low serum cortisol, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Partial recovery at time of publication
Sadao et al.	M	6	Fluticasone	Inhaled	Asthma	Ritonavir, Atazanavir, Tenofovir, Emtricitabine	11 months	Moon face, obesity, muscular atrophy, hypertension	Low serum cortisol, low serum ACTH	Directly stopped GC	Complete recovery 2 weeks after diagnosis

Sadarangani et al.	F	48	Triamcinolone	Intra-articular	Atopic dermatitis	Ritonavir, Atazanavir, Tenofovir, Emtricitabine	1 months	Moon face, weight gain	Low serum cortisol, low reaction to stimulation test	GC was already stopped at diagnosis	Complete recovery 2 months after diagnosis
Salvatore et al.	M	33	Triamcinolone	Intramuscular	Arthritis		2 months	Moon face, buffalo hump, striae, ecchymosis, obesity, muscular atrophy, skin thinning, hypertension	Low serum cortisol, low serum ACTH, low reaction to stimulation test, glycemic disorder	GC was already stopped at diagnosis, cortisol supplementation was used	Partial recovery at time of publication
Samaras et al. *#1*	M	43	Fluticasone	Inhaled	Asthma	Ritonavir, Didanosine, Amprenavir	2 years	Moon face, buffalo hump, striae, ecchymosis, obesity, muscular atrophy, weight gain	low urinary cortisol, low bone mineral density	Directly stopped GC, cortisol supplementation was used	Partial recovery at time of publication
Samaras et al. *#2*	M	43	Fluticasone	Inhaled	Asthma	Ritonavir, Atazanavir, Nevirapine	NK	Moon face, buffalo hump, obesity, muscular atrophy	low reaction to stimulation test, low bone mineral density	Directly stopped GC, cortisol supplementation was used	Complete recovery 6 months after diagnosis
Samaras et al. *#3*	M	53	Fluticasone	Inhaled	Asthma	Ritonavir, Lopinavir, Abacavir, Nevirapine	NK	Moon face, ecchymosis	Low serum cortisol, low urinary cortisol, low serum ACTH	Directly stopped GC	Partial recovery at time of publication
Samaras et al. *#5*	M	43	Fluticasone	Inhaled	Asthma	Ritonavir, Lopinavir, Abacavir	2 months	Moon face, ecchymosis, obesity, skin thinning	Low serum cortisol, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Partial recovery at time of publication
Samaras et al. *#6*	M	51	Fluticasone	Inhaled	Asthma	Ritonavir, Atazanavir, Lamivudine, Stavudine	2 months	Moon face, obesity, muscular atrophy	Low serum cortisol, glycemic disorder	Directly stopped GC	Complete recovery 4 months after diagnosis
Schwarze-Zander et al.	F	35	Triamcinolone	Intra-articular	Back pain	Ritonavir, Tenofovir, Emtricitabine, Saquinavir	2 months	Moon face, buffalo hump, oedema, obesity, muscular atrophy	Low serum cortisol, low serum ACTH	GC was already stopped at diagnosis	Complete recovery 6 months after diagnosis
Schweitzer et al.	F	46	Triamcinolone	Intra-articular	Other motive		5 weeks	Moon face, buffalo hump, striae, obesity, muscular atrophy	Low serum cortisol, low serum ACTH	GC was already stopped at diagnosis	Complete recovery 6 months after diagnosis
Semiz et al. *#1*	F	0.5	Clobetasol	Cutaneous	Diaper rash		2 months	Moon face, hypertrichosis, obesity, weight gain	Low serum cortisol, low serum ACTH	GC was switched to an other unknown corticoid, and then stopped	Partial recovery at time of publication
Semiz et al. *#2*	F	0.41	Clobetasol	Cutaneous	Diaper rash		4.5 months	Moon face, obesity, weight gain, hypertension	Low serum cortisol, low serum ACTH	GC was switched to an other unknown corticoid	Patient deceased
Seo et al.	F	25	Medroxyprogesterone	Unknown	Other motive		6 months	Moon face, hypertrichosis, obesity, muscular atrophy, hypertension	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC	Complete recovery 6 months after diagnosis
Siklar et al.	F	0.75	Clobetasol	Cutaneous	Diaper rash		3 months	Moon face, striae, ecchymosis	Low serum cortisol, low reaction to stimulation test	Unknown	Unknown outcome

Soldatos et al. *#2*	M	66	Fluticasone	Inhaled	Asthma	Ritonavir, Stavudine, Abacavir, Didanosine, Amprenavir	6 months	Moon face, buffalo hump, obesity, muscular atrophy, skin thinning, weight gain	low reaction to stimulation test, low bone mineral density	GC was switched to budesonide, cortisol supplementation was used	Partial recovery at time of publication
Song et al.	F	34	Triamcinolone, Dexamethasone	Multiple routes	Other motive	Ritonavir, Atazanavir, Tenofovir, Emtricitabine	1 month	Moon face, hypertrichosis, obesity, muscular atrophy	Low serum cortisol, low serum ACTH, low reaction to stimulation test	GC was already stopped at diagnosis, cortisol supplementation was used	Complete recovery 4 months after diagnosis
Spruyt et al. *#1*	M	48	Fluticasone	Inhaled	Asthma	Ritonavir, Lopinavir, Lamivudine, Zidovudine	1 month	Moon face, weight gain	Low serum cortisol, low serum ACTH	Directly stopped GC	Complete recovery 1 month after diagnosis
St Clair et al.	M	52	Fluticasone	Inhaled	Asthma	Ritonavir, Atazanavir, Efavirenz	2 days	Oedema, hypertension	Low serum cortisol, low serum ACTH, low reaction to stimulation test	GC treatment was maintained, and cortisol supplementation was used	Complete recovery, unknown delay
St Germain et al.	F	14	Fluticasone	Inhaled	Asthma	Ritonavir, Atazanavir, Tenofovir, Didanosine	0.5	Moon face, hypertrichosis, striae, oedema, muscular atrophy, weight gain	Low serum cortisol, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Complete recovery, unknown delay
Staughton et al. *#1*	F	53	Clobetasol	Cutaneous	Psoriasis		1 year	Moon face, buffalo hump, hypertrichosis, obesity, muscular atrophy, skin thinning, hypertension	Low serum cortisol, low reaction to stimulation test	GC was switched to an other unknown corticoid	Complete recovery 4 months after diagnosis
Staughton et al. *#2*	M	64	Clobetasol	Cutaneous	Psoriasis		10 weeks	Moon face, ecchymosis, skin thinning	Low serum cortisol, low reaction to stimulation test	GC was switched to an other unknown corticoid	Complete recovery 2 months and 1 week after diagnosis
Staughton et al. *#3*	M	63	Clobetasol	Cutaneous	Psoriasis		8 months	Moon face, striae, obesity, muscular atrophy	Low serum cortisol, low reaction to stimulation test	GC was switched to an other unknown corticoid	Complete recovery 3 weeks after diagnosis
Steven et al.	M	NK	Betamethasone	Nasal	Other motive		10 weeks	Moon face, striae, obesity, weight gain		Directly stopped GC	Partial recovery at time of publication
Teelucksingh et al.	F	9	Triamcinolone	Intralesional	Other motive		9 months	Moon face, buffalo hump, hypertrichosis, striae, obesity, weight gain	Low serum cortisol, low reaction to stimulation test	GC was already stopped at diagnosis, cortisol supplementation was used	Complete recovery 2 years after diagnosis
Tempark et al.	F	0.66	Triamcinolone, Clobetasol	Cutaneous	Diaper rash		NK	Moon face, striae, obesity, weight gain, hypertension	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Partial recovery at time of publication
Tsoukas et al.	F	61	Fluticasone	Inhaled	Asthma		NK	Ecchymosis, muscular atrophy, hypertension	low urinary cortisol, low serum ACTH, low reaction to stimulation test	GC was switched to ciclesonide, cortisol supplementation was used	Complete recovery 8 months after diagnosis
Tuel et al.	M	24	Triamcinolone	Epidural	Other motive		1 month	Moon face, buffalo hump	Low serum cortisol, low urinary cortisol	GC was already stopped at diagnosis	Partial recovery at time of publication

Ustyol et al.	M	4.25	fluorometholone	Ocular	Other motive		1 month	Moon face	Low serum cortisol, low serum ACTH, low reaction to stimulation test	Directly stopped GC	Complete recovery 4 months after diagnosis
Valin et al. *#1*	F	65	Fluticasone	Inhaled	Asthma	Ritonavir, Lopinavir	6 months	Moon face, striae, obesity, muscular atrophy, weight gain	Low serum cortisol, low bone mineral density	Directly stopped GC, cortisol supplementation was used	Complete recovery 6 months after diagnosis
Valin et al. *#2*	M	66	Fluticasone	Inhaled	Asthma	Ritonavir, Atazanavir	4 months	Moon face, buffalo hump, obesity, muscular atrophy, hypertension	Low serum cortisol, low serum ACTH, low reaction to stimulation test, low bone mineral density	Directly stopped GC, cortisol supplementation was used	Complete recovery 5 months after diagnosis
Valin et al. *#3*	M	66	Fluticasone	Inhaled	Asthma	Ritonavir, Lopinavir	2 years	Moon face, obesity, muscular atrophy	Low serum cortisol, low reaction to stimulation test, low bone mineral density, glycemic disorder	Directly stopped GC, cortisol supplementation was used	Partial recovery at time of publication
Valin et al. *#4*	F	29	Fluticasone	Inhaled	Asthma	Ritonavir, Lopinavir	1 month	Moon face, muscular atrophy, weight gain		GC treatment was maintained	Complete recovery 3 months after diagnosis
Valin et al. *#4bis*	F	29	Fluticasone	Inhaled	Asthma	Ritonavir, Lopinavir	2 weeks	Moon face, muscular atrophy, weight gain	Low serum cortisol, low reaction to stimulation test	Directly stopped GC, cortisol supplementation was used	Complete recovery 3 months after diagnosis
Verma et al. *#1*	M	0.66	Betamethasone	Oral	Asthma		6 months	Hypertrichosis, growth delay		Unknown	Unknown outcome
Vermeer et al.	F	8	Betamethasone	Cutaneous	Other motive		7.5 years	Moon face, buffalo hump, growth delay, hypertension	Low serum cortisol, low reaction to stimulation test	Directly stopped GC	Partial recovery at time of publication
Wilson et al.	F	59	Prednisolone, Fluticasone	Multiple routes	Asthma		2.5 years	Moon face, hypertrichosis, ecchymosis, muscular atrophy, hypertension	Low serum cortisol, low urinary cortisol, low reaction to stimulation test, low bone mineral density	GC was switched to budesonide	Complete recovery 7 months after diagnosis
Yoganathan et al.	F	48	Budesonide	Inhaled	Asthma	Ritonavir, Darunavir, Emtricitabine, Efavirenz	NK	Buffalo hump, striae, obesity, weight gain	Low serum cortisol, low reaction to stimulation test	Progressively stopped GC	Partial recovery at time of publication
Yombi et al. *#1*	F	54	Triamcinolone	Intra-articular	Arthritis	Ritonavir, Lopinavir, Lamivudine, Didanosine	2 weeks	Moon face, obesity, weight gain, hypertension	Low serum cortisol, low serum ACTH	GC was already stopped at diagnosis, cortisol supplementation was used	Complete recovery 8 months after diagnosis
Yombi et al. *#2*	M	56	Triamcinolone	Intra-articular	Arthritis	Ritonavir, Lamivudine, Stavudine, Indinavir	1 month	Moon face, muscular atrophy, weight gain	Low serum cortisol, low serum ACTH	GC was already stopped at diagnosis, cortisol supplementation was used	Complete recovery 4 months after diagnosis

Yombi et al. *#3*	F	49	Triamcinolone	Intra-articular	Arthritis	Ritonavir, Lamivudine, Zidovudine, Indinavir	2 months	Moon face, obesity, weight gain	Low serum cortisol, low serum ACTH	GC was already stopped at diagnosis	Complete recovery 5 months after diagnosis
Zil-E-Ali et al.	M	0.91	Triamcinolone	Cutaneous	Atopic dermatitis		3 months	Moon face, obesity, weight gain, growth delay, hypertension	Low serum cortisol, low reaction to stimulation test	Directly stopped GC	Complete recovery 2 months after diagnosis
Zubillaga et al.	F	48	Fluticasone	Inhaled	Asthma	Ritonavir, Lamivudine, Darunavir	36 months	Moon face, buffalo hump, hypertrichosis, striae, obesity, hypertension	Low serum cortisol	Directly stopped GC, cortisol supplementation was used	Partial recovery at time of publication

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Title of the thesis: Situations posing higher risk for Iatrogenic Cushing Syndrome: a Systematic Review and Cluster Analysis

Abstract :

Widely used, glucocorticoids nonetheless have many metabolic side effects impacting patient's quality of life, including iatrogenic Cushing syndrome, especially when used at high doses over a long period.

To identify situations and factors associated with an increased risk of iatrogenic Cushing syndrome, we performed a systematic review per PRISMA guidelines included multiple bibliographic databases (eg, PubMed/MEDLINE, Embase) spanning all dates of publication up to November 21.

A total of 211 articles were retrieved for full-text assessment. We included 147 articles in our review, for a total of 183 cases. Data extracted from them included age, gender, symptoms, drug administered, route of administration, and time between start of glucocorticoid treatment and diagnosis of iatrogenic Cushing syndrome. We performed a clustering analysis, identifying three distinct clusters. The first (n = 95) consisted of younger patients with diverse dermatologic disorders, ranging from atopic dermatitis (9%) to diaper rash (21%), using topical glucocorticoids like clobetasol (43%) or betamethasone (21%). The second (n = 32) included patients with rheumatologic disorders (31%) or back pain (22%) who were treated with repeated injections of steroids, usually triamcinolone (91%). The third (n = 56) included patients suffering from asthma (93%), taking inhaled glucocorticoids like fluticasone (86%) and antiretroviral therapies boosted by ritonavir (80%). We advise caution when prescribing glucocorticoids in these situations. Regular monitoring of symptoms is recommended for the prevention or early detection of iatrogenic Cushing syndrome.

KEYWORDS

CUSHING SYNDROME, IATROGENICITY, GLUCOCORTICOID, REVIEW, PHARMACOVIGILANCE

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Titre de la thèse : Syndrome de Cushing iatrogène et situations à risques : revue systématique de la littérature

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Résumé de la thèse :

Largement utilisés, les glucocorticoïdes ont néanmoins de nombreux effets secondaires métaboliques impactant la qualité de vie des patients, dont le syndrome de Cushing iatrogène, surtout lorsqu'ils sont utilisés à fortes doses sur une longue période.
Pour identifier les situations et les facteurs associés à un risque accru de syndrome de Cushing iatrogène, nous avons effectué une revue systématique de la littérature scientifique incluant plusieurs bases de données bibliographiques (PubMed/MEDLINE, Embase) jusqu'au 21 novembre.
Au total, 211 articles ont été récupérés pour l'évaluation du texte intégral. Nous avons inclus 147 articles dans notre revue, pour un total de 183 cas. Les données extraites de ces articles comprenaient l'âge, le sexe, les symptômes, le médicament administré, la voie d'administration et le délai entre le début du traitement par glucocorticoïdes et le diagnostic du syndrome de Cushing iatrogène. Nous avons effectué une analyse par clustering, et identifié trois groupes distincts. Le premier (n = 95) était composé de patients plus jeunes présentant divers troubles dermatologiques, allant de la dermatite atopique (9 %) à l'érythème fessier (21 %), et utilisant des glucocorticoïdes topiques comme le clobétasol (43 %) ou la bétaméthasone (21 %). La deuxième (n = 32) comprenait des patients souffrant de troubles rhumatologiques (31%) ou de douleurs dorsales (22%) qui étaient traités par des injections répétées de stéroïdes, généralement de la triamcinolone (91%). La troisième (n = 56) comprenait des patients souffrant d'asthme (93%), prenant des glucocorticoïdes inhalés comme la fluticasone (86%) et des trithérapies antirétrovirales boostées par ritonavir (80%). La prescription de glucocorticoïdes nécessite de bien connaitre les situations particulièrement à risque de syndrome de Cushing iatrogène. Une surveillance régulière des symptômes est recommandée pour la prévention ou la détection précoce du syndrome de Cushing iatrogène.

MOTS CLÉS

SYNDROME DE CUSHING, IATROGENIE, GLUCOCORTICOIDE, REVUE DE LA LITTERATURE, PHARMACOVIGILANCE

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