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ORIGINAL ARTICLE

Systemic glucocorticoid therapy: risk factors for reported adverse events and beliefs about the drug. A cross-sectional online survey of 820 patients

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Abstract Despite systemic glucocorticoids are widely used, risk factors for most of their adverse events and patients' beliefs about the drug are poorly known. An online survey was conducted between February and July 2013 through the website www.cortisone-info.fr. Demographic (e.g., age, gender) and therapeutic (e.g., type of prescribed glucocorticoid, duration of prescription) data were collected. Patients were further asked to answer questions about glucocorticoid-induced adverse events and their beliefs about efficacy and safety of the drug. Risk factors for adverse events and efficacy/safety beliefs were assessed using multivariate logistic regression models. Eight hundred twenty questionnaires were analyzed (women 74.3 %; median age 49 [34–62] years, median equivalent prednisone dosage 20 [10–48] mg/day). The most frequently reported adverse events were insomnia (n=477, 58.2 %), mood disturbances (n=411, 50.1 %), hyperphagia (n=402, 49.0 %), and lipodystrophy (n=387, 47.2 %). The risk of some adverse events (e.g., weight gain, easy bruising) increased with the duration of exposure while other adverse events (e.g., insomnia, mood disorders, epigastric pain) were present since the first days of exposure. The risk of hirsutism, altered wound healing, mood disturbances, weight gain, lipodystrophy, hyperphagia, and epigastric pain decreased with age. Cutaneous disorders, morphological changes, and epigastric pain were more frequently reported by women. Interestingly, patients prescribed prednisolone reported less adverse events than those prescribed prednisone. No adverse event, demographical or prescribing characteristics were associated with beliefs about efficacy while factors associated with safety concerns were age (OR: 1.2 [1.1–1.3] per 10-year increase), osteoporosis (OR: 3.3 [1.4–7.9]), easy bruising (OR: 1.6 [1.1–2.3]), insomnia (OR: 1.7 [1.2–2.4]), and weight gain (OR: 1.6 [1.1–2.2]). These results may help clinicians to adapt information speech, therapeutic education, and clinical and laboratory monitoring of patients prescribed glucocorticoid therapy.

Keywords Adverse events · Glucocorticoids · Online survey

Introduction

Taken by about 1 % of the population [1], glucocorticoids are the treatment of choice for numerous immunologic, rheumatologic, neoplastic, and allergic diseases. Sixty years after their discovery, glucocorticoids are still a drug widely used, although new treatments, like biotherapies, have emerged. Over the last 20 years, long-term systemic glucocorticoid prescriptions have increased by more than 30 % [1]. Unfortunately, long-term exposure to glucocorticoids is responsible for many adverse events such as osteoporosis, diabetes mellitus, or infections. After only a few weeks of exposure, disturbing adverse events are reported by about two thirds of patients [2]. These adverse events play an important role in reducing

The authors have full control of all primary data and agree that the journal can review their data upon request.

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patients' adherence [3, 4]. Moreover, they are frequently life-threatening, and glucocorticoids have been shown as the most common specific cause of adverse events requiring hospitalization in the USA [5]. They further entail a significant cost to the health system [6]. Despite their frequency, cost, and impact on patients' daily living or treatment adherence, few studies have focused on the epidemiological aspects of most of the glucocorticoid-induced adverse events. Excluding osteoporosis, diabetes mellitus, and infections for which some epidemiological evidences are available, the incidence, risk factors, and natural history of many of the other adverse events (e.g., lipodystrophy, hypertension, neuropsychiatric, or cutaneous disorders) are surprisingly sparse even though they are considered by patients as the most inconvenient [7–9]. In this context, the aims of this study were (1) to assess whether characteristics of the patients (i.e., age and gender) or of the glucocorticoid exposure (i.e., duration of exposure and type of prescribed glucocorticoid) were risk factors for these adverse events and (2) whether glucocorticoid-induced adverse events were associated with beliefs regarding glucocorticoid efficacy and safety.

Materials and methods

Online questionnaire

Patients visiting the medical website www.cortisone-info.fr during a 6-month period (February–July 2013) were asked whether they would be willing to participate to an online study regarding glucocorticoid-induced adverse events. Those who agreed to participate were asked to fill out an online questionnaire. The website www.cortisone-info.fr, created in 2012, aims to inform patients and their relatives about glucocorticoids. It is made of 43 pages about five themes: generalities about glucocorticoids, adverse events, associated measures, modalities of treatment withdrawal, and particular situations. Pages about adverse events are the most visited [10]. The website is recognized by the French High Authority of Health. It is not sponsored by pharmaceutical. The questionnaire was online between February and July 2013. Patients were informed that their responses would be anonymous and would be used for scientific purposes. The questionnaire included 22 questions with single or multiple choices on which the first 14 were used for this study (supplementary file). It was divided into three parts. The first was interested in patient characteristics (i.e., age, sex, weight) and glucocorticoid therapy (i.e., current and maximum dosages, underlying disease, specialty of the prescriber, name of the prescribed glucocorticoid, and duration of the prescription). In the second part, patients were questioned about the symptoms they thought to be associated with the glucocorticoid exposure. The third part questioned patients about their beliefs regarding efficacy and safety of glucocorticoids. Regarding these beliefs, patients were asked to answer two questions with four items each (very ineffective, rather ineffective, rather effective, or very effective for evaluation of efficacy; very harmless, rather harmless, rather dangerous, or very dangerous for evaluation of safety). The items "very ineffective" and "rather ineffective" on one hand and "rather effective" and "very effective" on the other hand were combined in order to define beliefs about efficacy. The items "very harmless"/"rather harmless" and "rather dangerous"/"very dangerous" were also combined to define beliefs about safety. Patients were asked to complete the questionnaire only once. Patients treated with intra-muscular, intra-articular, inhaled, or cutaneous glucocorticoids or who were taking glucocorticoids for adrenal insufficiency were excluded.

Statistical analysis

The first purpose of this study was to describe the prevalence of the main glucocorticoid-induced adverse events according to the duration of exposure in order to identify the adverse events occurring since the first days of exposure and those occurring later. The second purpose was to compare the characteristics of patients reporting a given adverse event to these of patients not reporting the event. Risk factors for each adverse event of interest were assessed using multivariate logistic regression models. The independent contributions to the outcome were assessed for four variables: age, gender, duration of exposure, and the type of prescribed glucocorticoid (i.e., prednisone, prednisolone, or other). Models were adjusted on diseases for which glucocorticoids were prescribed, on specialty of the prescriber (e.g., general practitioner, pneumologist, internal medicine physician) and on prednisone equivalent daily dosage taken at the time the patients filled out the questionnaire. For age, we checked linearity by comparing two models: one with the linear term and the other with the categories using the log likelihood ratio test. We thus evidenced that age could be included in the models as a continuous variable. We arbitrarily chose to categorize the duration of exposure into four categories, best reflecting clinical practice (i.e., <2 weeks of exposure, 2 weeks to 3 months, 3–6 months, and >6 months). In the third part of this study, multivariate logistic regression models were used to assess whether age, gender, duration of prescription, underlying disease, type of prescribed glucocorticoid, or any adverse events were associated with a feeling of efficacy or safety of the glucocorticoid therapy. All adverse events were included in the models, and the final multivariate results were obtained by using a backward stepwise procedure based on log-likelihood ratio to eliminate nonsignificant ($p>0.05$) variables from the initial model. No interaction terms were included in the models. P values of less than 0.05 were considered significant, and values were expressed as odds ratio (OR) with 95 % CI.

For descriptive analysis, quantitative variables are described by median and quartiles 25 and 75 while qualitative variables are expressed as a percentage. Statistical analysis was carried out by using Stata, version 11.2 (StataCorp, College Station, TX)

Results

Study population

During the study period, 1004 patients answered the questionnaire among whom 184 were excluded from the analysis because of incomplete data (n=104), unsuitable route of administration (n=69), or glucocorticoids taken for adrenal insufficiency (n=11). The characteristics of the 820 remaining patients are summarized in Table 1. The median age of these patients was 49 years [34–62], and 74.3 % of them were women. Most patients were taking prednisone (n=483, 58.9 %) or prednisolone (n=262, 32.0 %). The median daily prednisone equivalent dosage taken by patients at the time of questionnaire was 20 [10–48] mg. The reasons for glucocorticoid prescriptions were various, rheumatic diseases being the most frequent. Most of the people who answered the questionnaire were chronically exposed to glucocorticoids, 442 (53.9 %) of them taking glucocorticoids for more than 3 months. Prescribers were primarily general practitioners (n=178, 21.7 %), rheumatologists (n=163, 19.9 %), and internists (n=109, 13.3 %).

Reported adverse events and timing of occurrence

Among those who answered the questionnaire, only 4.8 % (n=40) reported no adverse event they imputed to glucocorticoids (Table 2). The most frequently reported adverse events were neuropsychiatric disorders (e.g., insomnia, mood disorders), morphological disorders (e.g., lipodystrophy, weight gain), and skeletal/muscular disorders (e.g., muscle cramps, muscle weakness), reported respectively by more than 40 % of the patients (Table 2). The risk of some adverse events (e.g., weight gain, lipodystrophy, easy bruising) increased with the duration of exposure while other adverse events (e.g., insomnia, mood disorders, epigastric pain) were present since the first days of exposure (Table 2).

Risk factors for adverse events

Some risk factors for adverse events, such as diabetes, were not assessed due to a small number of patients reporting the outcome and the risk of the models being overloaded. Risk factors for the other adverse events are reported in Tables 3, 4, and 5. For some adverse events (e.g., cutaneous disorders and weight gain), a positive linear association with the duration of glucocorticoid exposure was evidenced. For some others (e.g., insomnia, mood disturbances), there was no association with the time of exposure. Age and gender were found to be risk factors for several adverse events. Except for osteoporosis and lower limb edema, the risk of adverse events decreased with age. On the other hand, hirsutism, spontaneous bruising, lipodystrophy, weight gain, and epigastric pain were more frequently reported by women. Interestingly, the type of prescribed glucocorticoid was associated with the risk of reporting adverse events. Prednisolone was less frequently associated with adverse events (e.g., insomnia, mood disturbances, lipodystrophy, weight gain, hyperphagia, muscle cramps, osteoporosis) than prednisone.

Table 1 Characteristics of the study population

	Patients n=820
Median age [25–75 IQR], years	49 [34–62]
Female, n (%)	609 (74.3)
Underlying disease	
Systemic vasculitis, n (%)	130 (15.9)
Rheumatoid arthritis, n (%)	93 (11.3)
Ear-nose-throat (ENT) diseases, n (%)[a]	84 (10.2)
Other rheumatic diseases, n (%)[b]	76 (9.3)
Inflammatory bowel diseases, n (%)	73 (8.9)
Connective tissue diseases, n (%)	64 (7.8)
Lung diseases, n (%)[c]	63 (7.7)
Others, n (%)	237 (28.9)
Median equivalent prednisone dosage [25–75 IQR] (mg)	20 [10–48]
Drug	
Prednisone, n (%)	483 (58.9)
Prednisolone, n (%)	262 (32.0)
Others, n (%)[d]	75 (9.1)
Prescriber	
General practitioner, n (%)	178 (21.7)
Rheumatologist, n (%)	163 (19.9)
Internist, n (%)	109 (13.3)
Pneumologist, n (%)	81 (9.9)
Gastroenterologist, n (%)	69 (8.4)
Neurologist, n (%)	37 (4.5)
Nephrologist, n (%)	27 (3.3)
Others, n (%)[e]	156 (19.0)
Duration of treatment	
<2 weeks	200 (24.4)
2 weeks to 3 months	166 (20.2)
3 to 6 months	90 (11.0)
>6 months	364 (44.4)

[a] e.g., sinusitis, otitis, laryngitis

[b] e.g., sciatica, arthrosis, cervicobrachial neuralgia

[c] Mainly asthma and COPD

[d] i.e., methylprednisolone, dexamethasone, triamcinolone

[e] i.e., oncologist, hematologist, ENT, allergist, dermatologist

Table 2 Prevalence of reported glucocorticoid-induced adverse events according to duration of exposure

	<15 days *n*=200	15 days–3 months *n*=166	3–6 months *n*=90	>6 months *n*=364
Median number of reported adverse events	2.5 [1–4]	4 [3–7]	6 [4–8]	6 [4–8]
Number of patients reporting no adverse events, *n* (%)	27 (13.5)	8 (4.8)	0 (0)	5 (1.4)
Adverse events with prevalence quite stable over time				
Insomnia, *n* (%)	110 (55.0)	109 (65.7)	49 (54.4)	209 (57.4)
Mood disorders, *n* (%)	84 (42.0)	84 (50.6)	47 (52.2)	196 (53.8)
Epigastric pain, *n* (%)	47 (23.5)	48 (28.9)	19 (21.1)	104 (28.6)
Hypertension, *n* (%)	31 (15.5)	28 (16.9)	7 (7.8)	68 (18.7)
Adverse events with prevalence increasing over time				
Hyperphagia, *n* (%)	62 (31.0)	102 (61.4)	54 (60.0)	184 (50.4)
Lipodystrophy, *n* (%)	38 (19.0)	70 (42.2)	62 (68.9)	217 (60.1)
Weight increase, *n* (%)	21 (10.5)	48 (28.9)	45 (50.0)	207 (59.6)
Diabetes, *n* (%)	6 (3.0)	5 (3.0)	4 (4.4)	18 (4.9)
Tremors, *n* (%)	39 (19.5)	54 (32.5)	33 (36.7)	95 (26.1)
Muscle weakness, *n* (%)	37 (18.5)	53 (31.9)	29 (32.2)	145 (39.8)
Muscle cramps, *n* (%)	40 (20)	67 (40.4)	49 (54.4)	181 (49.7)
Lower limb edema, *n* (%)	16 (8.0)	24 (14.5)	18 (20.0)	82 (22.5)
Easy bruising, *n* (%)	17 (8.5)	33 (19.9)	26 (28.9)	169 (46.4)
Hirsutism, *n* (%)	6 (3.0)	27 (16.3)	29 (32.2)	130 (35.7)
Altered wound healing, *n* (%)	4 (2.0)	17 (10.2)	22 (24.4)	87 (23.9)
Osteoporosis, *n* (%)	4 (2.0)	3 (1.8)	4 (4.4)	51 (14.0)
Aseptic osteonecrosis, *n* (%)	1 (0.5)	1 (0.6)	1 (1.1)	16 (4.4)
Menstrual disorders, *n* (%)[a]	8 (8.3)	9 (16.1)	17 (48.6)	37 (30.3)

[a] Among the 317 women<50 year old

Beliefs about glucocorticoids

Among the 794 patients who completed items regarding their beliefs about glucocorticoids, 683 (86.0 %) considered glucocorticoids as efficient and 542 (68.3 %) considered they were unsafe. No adverse event, demographical or prescribing characteristics (in particular, the type of prescribed glucocorticoid was not significantly associated with a feeling of efficacy, OR: 0.8 [0.5–1.3], p=0.38 for the comparison prednisolone versus prednisone) were associated with beliefs about efficacy. On the other hand, factors significantly associated with the belief that glucocorticoids were unsafe were age (OR: 1.2 [1.1–1.3] per 10-year increase, p<0.001), reported osteoporosis (OR: 3.3 [1.4–7.9], p=0.007), easy bruising (OR: 1.6 [1.1–2.3], p=0.02), insomnia (OR: 1.7 [1.2–2.4], p=0.001), and weight gain (OR: 1.6 [1.1–2.2], p=0.01).

Discussion

The present study based on an online survey of 820 glucocorticoid-exposed patients evidences that the risk of some adverse events (e.g., hirsutism, weight gain, easy bruising) increases with the duration of exposure while others such as insomnia, mood disturbances, or epigastric pain are present from the first days of exposure. Except for osteoporosis and lower limb edema, the risk of adverse events decreases with age. Women are also more likely than men to report adverse events. Noteworthy, prednisolone appears to cause fewer adverse events than prednisone. Finally, beliefs about safety of glucocorticoids are related to age and presence of some adverse events.

Adverse events reported by the study participants were mainly skin, morphological, and neuropsychiatric disorders, reported by nearly half of them. Even though our study population (i.e., a population of patients visiting websites and answering online questionnaires) is likely to be different from the overall population of patients prescribed glucocorticoids, our results are nevertheless quite similar to those found in other studies. In a mailed survey of 2446 US patients, Curtis et al. found that 90 % of patients exposed to systemic glucocorticoids for a mean time of 284±177 days reported at least one adverse event they imputed to the drug [11]. Weight gain (70 %), skin bruising or thinning (more than 55 % of patients), and sleep disturbances (nearly 50 % of the patients) were the most commonly reported adverse events. In a previous prospective study, we found that after 3 months of systemic glucocorticoid exposure, lipodystrophy was reported by 63 % of

Table 3 Risk factors for cutaneous and neuropsychiatric adverse events

	Hirsutism		Altered wound healing		Easy bruising		Insomnia		Mood disturbances		Tremors	
	OR [95 % CI]	*p*	OR [95 % CI]	*p*	OR [95 % CI]	*p*	OR [95 % CI]	*p*	OR [95 % CI]	*p*	OR [95 % CI]	*p*
Age (per 10-year increase)	0.7 [0.6–0.8]	<0.001	0.9 [0.8–1.0]	0.04	1.1 [0.9–1.2]	0.28	0.9 [0.8–1.0]	0.22	0.8 [0.7–0.9]	<0.001	0.9 [0.8–1.1]	0.36
Sex (female versus male)	2.5 [1.6–4.1]	<0.001	1.3 [0.8–2.1]	0.28	2.2 [1.5–3.4]	<0.001	1.0 [0.7–1.5]	0.79	1.0 [0.7–1.4]	0.87	0.8 [0.6–1.2]	0.34
Duration of prescription												
<2 weeks	1	–	1	–	1	–	1	–	1	–	1	–
2 weeks–3 months	5.3 [1.9–14.5]	0.001	3.4 [1.0–11.1]	0.04	1.9 [0.9–4.0]	0.07	1.5 [0.9–2.4]	0.15	1.3 [0.8–2.2]	0.31	1.7 [1.0–3.1]	0.06
3–6 months	13.7 [4.9–38.5]	<0.001	10.9 [3.4–35.4]	<0.001	3.1 [1.4–6.8]	0.005	1.1 [0.6–2.0]	0.79	1.4 [0.8–2.6]	0.26	2.4 [1.2–4.7]	0.01
>6 months	17.6 [6.9–45.3]	<0.001	9.5 [3.2–28.6]	<0.001	6.4 [3.3–12.4]	<0.001	1.2 [0.7–1.9]	0.50	1.3 [0.8–2.1]	0.22	1.5 [0.8–2.6]	0.17
Type of glucocorticoid												
Prednisone	1	–	1	–	1	–	1	–	1	–	1	–
Prednisolone	0.7 [0.4–1.2]	0.18	0.7 [0.4–1.2]	0.24	0.7 [0.4–1.1]	0.10	0.6 [0.4–0.9]	0.01	0.6 [0.4–0.9]	0.008	0.7 [0.5–1.1]	0.16
Others	1.4 [0.7–2.8]	0.40	0.9 [0.4–2.0]	0.80	1.0 [0.5–1.9]	0.95	0.6 [0.3–1.0]	0.05	0.8 [0.5–1.5]	0.53	1.0 [0.5–1.8]	0.39

Table 4 Risk factors for morphological and endocrine adverse events

	Lipodystrophy		Weight gain		Lower limb edema		Increase of blood pressure		Menstrual disorders		Hyperphagia	
	OR [95 % CI]	*p*	OR [95 % CI]	*p*	OR [95 % CI]	*p*	OR [95 % CI]	*p*	OR [95 % CI]	*p*	OR [95 % CI]	*p*
Age (per 10-year increase)	0.8 [0.7–0.9]	0.001	0.8 [0.7–0.9]	<0.001	1.1 [1.0–1.3]	0.06	1.1 [0.9–1.2]	0.29	0.6 [0.4–0.7]	<0.001	0.8 [0.7–0.9]	<0.001
Sex (female versus male)	2.5 [1.7–3.7]	<0.001	1.6 [1.1–2.4]	0.02	1.6 [1.0–2.5]	0.07	0.9 [0.6–1.5]	0.81	–	–	1.0 [0.8–1.6]	0.64
Duration of prescription												
<2 weeks	1	–	1	–	1	–	1	–	1	–	1	–
2 weeks–3 months	2.8 [1.6–5.0]	<0.001	3.2 [1.6–6.2]	0.001	1.3 [0.6–3.0]	0.46	1.1 [0.6–2.1]	0.77	2.0 [0.7–6.1]	0.22	3.7 [2.1–3.6]	<0.001
3–6 months	13.7 [6.7–28.0]	<0.001	9.5 [4.5–20.1]	<0.001	2.4 [1.0–5.5]	0.04	0.6 [0.2–1.4]	0.23	8.7 [2.9–26.3]	<0.001	3.1 [1.7–6.0]	<0.001
>6 months	7.8 [4.4–13.6]	<0.001	12.3 [6.4–23.5]	<0.001	2.2 [1.1–4.4]	0.02	1.3 [0.7–2.3]	0.42	4.7 [1.7–12.7]	0.002	2.2 [1.3–3.5]	0.002
Type of glucocorticoid												
Prednisone	1	–	1	–	1	–	1	–	1	–	1	–
Prednisolone	0.6 [0.4–0.9]	0.02	0.6 [0.4–0.9]	0.01	0.6 [0.4–1.1]	0.10	1.0 [0.6–1.6]	0.91	0.9 [0.5–1.8]	0.78	0.5 [0.4–0.8]	0.001
Others	1.6 [0.9–2.8]	0.12	0.9 [0.5–1.6]	0.64	1.1 [0.6–2.2]	0.76	1.5 [0.8–2.8]	0.25	0.6 [0.2–2.3]	0.44	0.9 [0.5–1.6]	0.68

Table 5 Risk factors for muscular/skeletal adverse events and epigastric pain

	Muscle cramps		Muscle weakness		Osteoporosis		Epigastric pain	
	OR [95 % CI]	*p*	OR [95 % CI]	*p*	OR [95 % CI]	*p*	OR [95 % CI]	*p*
Age (per 10-year increase)	1.0 [0.9–1.1]	0.62	0.9 [0.8–1.0]	0.28	1.2 [1.0–1.5]	0.09	0.9 [0.8–1.0]	0.04
Sex (female versus male)	1.1 [0.8–1.6]	0.47	0.9 [0.6–1.3]	0.59	1.0 [0.5–1.8]	0.88	1.7 [1.1–2.6]	0.01
Duration of prescription								
<2 weeks	1	–	1	–	1	–	1	–
2 weeks–3 months	2.1 [1.2–3.7]	0.008	1.8 [1.0–3.3]	0.04	0.5 [0.1–2.3]	0.34	1.6 [0.9–2.8]	0.11
3–6 months	4.3 [2.2–8.2]	<0.001	1.9 [1.0–3.7]	0.06	1.2 [0.3–5.6]	0.79	1.4 [0.7–2.9]	0.32
>6 months	3.3 [2.0–5.6]	<0.001	2.4 [1.4–4.1]	0.001	4.0 [1.3–12.5]	0.02	1.9 [1.1–3.1]	0.02
Type of glucocorticoid								
Prednisone	1	–	1	–	1	–	1	–
Prednisolone	0.7 [0.5–1.0]	0.05	0.7 [0.5–1.1]	0.09	0.4 [0.2–0.9]	0.03	1.1 [0.7–1.6]	0.78
Others	1.7 [1.0–3.1]	0.05	1.0 [0.6–1.7]	0.96	1.0 [0.4–2.9]	0.95	1.3 [0.7–2.4]	0.35

the patients and neuropsychiatric and cutaneous disorders by 52 and 46 % of them, respectively [2]. During the first 3 months of exposure, 66 % of patients reported at least one distressing adverse events.

In our study, women reported more cutaneous and morphological adverse events than men. This is in accordance with the sparse available data. In a previous prospective study, we found that women were significantly more likely to develop lipodystrophy (OR: 4.2 [1.2–14.7], $p=0.02$) and skin disorders (OR: 6.0 [1.2–29.3], $p<0.01$) [2]. Hirsutism is probably more rapidly apparent in women than in men. On the other hand, women may be more concerned with morphological changes such as lipodystrophy or weight gain than are men and therefore may be more likely to report them. However, using photographs of patients, we previously objectified a 10-fold higher risk of lipodystrophy in women than in men [12]. We also found that the risk of reported glucocorticoid-induced adverse events decreases with age. While this has already been evidenced for some adverse events such as morphological changes [12], the results are more surprising regarding altered wound healing and mood disturbances. In a previous study of more than 370,000 patients exposed to systemic glucocorticoids, the risk of depression, mania, and confusion/delirium increased with age contrary to this of panic disorders or suicidality [13]. On the other hand, in the daily practice, altered wound healing seems more frequent in the elderly, even though this has never been demonstrated. Considering age as a surrogate marker for the glucocorticoid dose and the underlying disease, a paradoxical relation for age cannot be totally ruled out.

There is some available evidence regarding the relationship between daily or cumulative glucocorticoid dosage and occurrence of adverse events [11, 14], but, to our knowledge, there is very little available evidence regarding the relationship between risk of adverse events and duration of exposure, except maybe for osteoporosis. We therefore chose to focus our analyses on exposure duration rather than on cumulative dosage. Our purpose was to assess whether some glucocorticoid-induced adverse events occur since the first days of exposure or only after several weeks or months of treatment, this information being useful for prescribers in order to better inform (and reassure?) the patients exposed only for a few days or week to the drug. As Huscher et al. previously did for the relationship between daily dosage and the risk of adverse events [14], we evidenced two distinct time-related patterns: a "linear" rising with duration of exposure (e.g., cutaneous disorders and weight gain) and a "threshold" pattern with an increased risk of adverse events since the first days of exposure. The threshold pattern may probably be explained by the fact that, when adverse events such as insomnia or mood disturbances occur, they occur during the first days of exposure, with no more occurrence thereafter. These adverse events can therefore occur in patients prescribed short-term glucocorticoid therapy who should be adequately informed.

Interestingly, we found that many adverse events were less frequently reported by patients prescribed prednisolone as compared to those prescribed prednisone. To our knowledge, the occurrence of adverse events according to the molecule used has never been previously studied. Pharmacologically, prednisolone is the active substance, whereas the inactive prednisone is metabolized by liver to prednisolone. However, the bioavailability of prednisone (about 80 %) is significantly better than this of prednisolone [15, 16]. Thus, it can be argued that prednisolone induces fewer adverse events because of a lower bioavailability, being therefore also less efficient. However, in our study, the feeling of efficacy reported by patients did not differ from a molecule to another. Since, without any apparent scientific basis, the molecules that are prescribed vary between countries (prednisone being for instance much more prescribed in France and in the USA and prednisolone

being much more used in the UK [1, 2, 11, 17]), comparative studies are needed to assess whether one or the other of these molecules, usually presented as equivalent, is actually more efficient and/or iatrogenic.

Glucocorticoids were acknowledged as efficient by most of the patients, but they were also considered as unsafe by more than two thirds of them. Similarly, Ludici et al. found that 84 % of patients with systemic sclerosis believed in the necessity of glucorticoids for maintaining health but 73 % also reported concerns about potential adverse events [18]. In the same way, the study by Zerah et al. evidenced that 83 (46 %) out of 181 patients on long-term glucocorticoid therapy reported that glucocorticoids were more dangerous than efficient [3]. In this study, concerns about safety were strongly associated with a lower adherence to the drug [3]. In taking into account patients' worries and concerns, adequate therapeutic education would probably increase adherence to glucocorticoids.

Our study has several strengths. Among them are the large number of patients recruited all over France, the wide patterns of glucocorticoid therapies that the patients were receiving at the time of the study, and the availability of data regarding adverse events often considered as "minors" and for which no epidemiological data were available. Another strength is the use of internet for questioning patients. Fast and free, online surveys facilitate the collection and management of data. We also believe that it increases external validity as it allows investigating outpatients or those with very short time glucocorticoid exposure, sometimes hard to reach for scientific purposes. Nevertheless, our work has also several limitations. The first one is that the results are based on a selected population of patients (i.e., patients visiting websites and answering online questionnaires), who is likely to be different from the overall glucocorticoid-exposed population. We know that patients usually visit our website when they notice a new symptom or when they feel insufficiently informed about their treatment. Thus, the prevalence of adverse events cannot be considered as reflecting the prevalence of adverse events of all patients prescribed glucocorticoids. Nevertheless, regarding assessment of risk factors for adverse events and beliefs about the drug, we believe that the large sample of patients who responded to the questionnaire provides enough variation in the data to make our conclusions relevant. Another shortcoming in this study was the cross-sectional assessment of some variables such as daily dosage. Patients were asked to report the daily glucocorticoid dosage they were receiving at the time they filled out the questionnaire. However, the adverse events may have occurred many weeks before, at a different dosage. Further, to improve estimates of the impact of glucocorticoid exposure on the occurrence of adverse events, it would have been of interest to obtain the cumulative dosage at time of adverse events occurred which was difficult owing to the cross-sectional, online design of our study. Noteworthy, the association between daily dosage and occurrence of some glucocorticoid-induced adverse events has already been studied in large populations [11, 14]. Further, it is likely that some confounding factors were not taken into account in the analyses. For instance, it would have been interesting to have data about dietary intakes for metabolic disorders or past psychiatric history for mood disturbances but, by greatly increasing the time required to complete the questionnaire, this would have reduced the feasibility of the study. Finally, it can be argued that the declarative assessment of adverse events could have led to a poor reliability of the results. However, many of the adverse events we studied (e.g., insomnia, mood disturbances, epigastric pain, and hyperphagia) are, by nature, declaratives. When these adverse events are evaluated face to face, physicians do nothing more than what we did in this study, i.e., questioning patients about the presence or absence of a symptom.

In conclusion, this online study may help physicians to adapt information speech, therapeutic education, and clinical and laboratory monitoring throughout the treatment according to the patient profile. By taking into account the glucocorticoid-induced adverse events (in particular those considered as minors by physicians but very frequently reported by the patients and associated with concerns about the drug), we can hope improving the beliefs about the drug and therefore the treatment adherence.

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