Quantifying cutaneous adverse effects of systemic glucocorticoids in patients with rheumatoid arthritis: a cross-sectional cohort study

J. Amann[1] & A.-M. Wessels[2], F. Breitenfeldt[1], D. Huscher[3], J.W. J. Bijlsma[2], J.W. G. Jacobs[2] & F. Buttgereit[1]

[1]Department of Rheumatology and Clinical Immunology, Charité University Medicine, Berlin, Germany; [2]Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, the Netherlands; [3]German Rheumatism Research Center Berlin, Epidemiology, Berlin, Germany.

Abstract

Objective

EULAR guidelines state that adverse effects (AEs) of glucocorticoid (GC) therapy should be considered and discussed with the patient before treatment is initiated. However, reliable quantitative data, especially on cutaneous AEs of low-to-medium dose GCs are lacking. We performed a study assessing the occurrence of cutaneous AEs of GCs and its association with current and cumulative GC doses in patients with rheumatoid arthritis (RA).

Methods

In a cross-sectional study performed in 2 outpatient rheumatology centres, 381 RA patients were enrolled. They were classed into 4 groups, according their mean daily dose during the past 12 months: 0 mg (n=87), <5mg (n=108), 5–7.5 mg (n=130), and >7.5 mg (n=56) of prednisone equivalent. AEs of GC on the skin were assessed by physical examination using a predefined scoring system, and by patients' self-assessments. Data were analysed according GC dose categories and cumulative doses.

Results

Cushingoid habitus, easy bruising, skin atrophy, and impaired wound healing as reported by patients occurred significantly more frequently in those using a GC the past 12 months, compared to those not using a GC. At physicians' assessments, only Cushingoid habitus and ecchymosis were more prevalent in GC users. The prevalence of these AEs was statistically significantly positively associated with current and cumulative GC dose. There was low occurrence of abnormal stretch marks, acne, perioral dermatitis, alopecia and hirsutism, which were not correlated with GC use.

Conclusion

Certain GC-associated cutaneous AEs are common in RA, but other AEs of GC occur infrequently at the low-to-medium GC doses used in RA.

Key words

glucocorticoid, adverse effect, side effect, skin, atrophy, Cushingoid, physical examination, patient assessment, rheumatoid arthritis

*Jonna Amann, MD, PhD**
*Anne-Marie Wessels, MD**
Friederike Breitenfeldt, MD, PhD
Dörte Huscher, PhD
Johannes W. J. Bijlsma, MD, PhD
*Johannes W. G. Jacobs, MD, PhD***
*Frank Buttgereit, MD, PhD***

**These two authors contributed equally sharing first authorship;*
***these two authors contributed equally sharing last authorship.*

Please address correspondence to:
Dr J.W.G. Jacobs,
University Medical Center Utrecht,
3508 GA Utrecht, The Netherlands.
E-mail: j.w.g.jacobs@umcutrecht.nl

Received on July 5, 2016; accepted in revised form on November 10, 2016.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2017.

Competing interests: the authors did not receive any financial or material support for this research.
F. Buttgereit reported receiving consultancy fees, honoraria, and travel expenses from Horizon Pharma and Mundipharma Int Ltd., and grant support from Horizon Pharma.
J.W.J. Bijlsma reported receiving honoraria from Mundipharma Int Ltd. and Sun.
J. Amann, A.-M. Wessels, F. Breitenfeldt, D. Huscher, and J.W.G. Jacobs have declared no competing interests.

Introduction

Glucocorticoids (GCs) are potent anti-inflammatory and immunosuppressive drugs successfully used to treat various diseases by general physicians and specialists. Their use has increased over the past 20 years and is estimated at 0.8–1.2% of the population in developed countries (1, 2). In early rheumatoid arthritis (RA), GCs have been proven to have symptomatic and disease-modifying properties (3, 4); 49% of Swedish and 56% of German patients with RA are treated with GCs (5, 6), and phase II–IV RA trials on biological drugs reported concomitant treatment with GCs in 39-70% of patients (5). In the European League against Rheumatism (EULAR) recommendations on systemic low and medium GC therapy, recommendation is to inform patients about adverse effects (AEs) and to discuss these before the therapy is started (7, 8). This is fully in line with the contemporary trend of shared decision making with the patient. However, systemic literature reviews have demonstrated that data on most AEs are very scarce (9, 10); therefore another EULAR recommendation is that AEs of GCs should systemically be assessed in trials (11). There are data regarding the risk of infections, diabetes and osteoporosis, but data on AEs on the skin of low and low-to-medium systemic GC therapy are virtually lacking. Patients and physicians may not realise that both spectrum and prevalence of AEs on the skin of low-to-medium dose GC therapy are probably much smaller and lower than the spectrum and prevalence of the well-known and feared AEs of high GC dosages (7, 9). This might in daily clinical practice hamper initiation and continuation of even low GC doses. The aim of this study was to fill this gap in knowledge by collecting quantitative data on the AEs of GCs on the skin, enabling to better inform patients on this therapy, according to international guidelines and good clinical practice.

Patients and methods

Patients

Participants were recruited at the rheumatology outpatient departments of the Charité University Medicine Berlin (centre 1) and the University Medical Center Utrecht (centre 2) from April 2012 to March 2013. All patients aged ≥18 years, diagnosed with RA according to the American College of Rheumatology criteria (1987 or 2010), who regularly visited one of the two out patient departments, were invited to participate.

Study design

It was an outpatient clinic-based, cross-sectional cohort study, which was approved by the respective ethics committees. The medical history, including drug usage, and the 28-joint Disease Activity Score (DAS28) were assessed as part of routine clinical care. Furthermore, demographic and disease-related information as well as comorbidities such as diabetes and obesity were recorded. In addition, patients filled out a self-assessment questionnaire on AEs of GCs on the skin, and underwent an extended, targeted physical examination looking for signs that could be AEs of GCs on the skin.

To obtain more comprehensive results, each of the two centres recruited patients by a different method. To quantify the actual distribution of GC doses, the patients from centre 1 were randomly selected consecutively as they visited the outpatient clinic. Patients were classed into 4 groups, according to their mean daily dose during the past 12 months: 0 mg (n=87), <5 mg (n=108), 5–7.5 mg (n=130), and >7.5 mg (n=56) of prednisone equivalent. To get four equally sized groups in all these four dose categories for proper statistical analyses, patients from centre 2 were selected by their mean daily GC intake during the past 12 months. The patients' specific mean daily GC dose during the past 12 months was calculated using information from the patients' written or digital records, which was verified by patient interview. Short-term high GC doses (*i.e.* daily doses of >50 mg prednisone equivalent) were included in the calculation. Also, the lifelong cumulative dose of GC was calculated for all patients.

Signs that could be AEs of GCs on the skin, assessed both by patients' self-assessment and targeted physical examination were Cushingoid appearance, abnormal stretch marks (striae cutis

distensae), acne, perioral dermatitis, hirsutism, and thinning of scalp hair/alopecia. Ecchymosis was assessed by physical examination only and easy bruising, skin atrophy, and impaired wound healing were assessed by patients' self-assessment only. Acne was scored without differentiation into types, and we used a visual analogue scale (VAS) patients on impact of acne and the global acne grading system (GAGS) (12) for scoring the distribution of the lesions; the full scoring system is described in the supplement file. Thinning of scalp hair/alopecia was scored with a VAS patients, the Hamilton-Norwood scale for male pattern baldness (13, 14), and the Ludwig scale for female pattern baldness (15). Perioral dermatitis was scored using a modified version of the Perioral Dermatitis Severity Index (PODSI) (16, 17), and hirsutism by a modified Hirsutism-Score (18, 19). To ensure a similar physical exam approach, prior to the study start, examiners from both centres examined RA patients together; furthermore, a predefined definition and scoring system was used for signs that could be AEs of GCs on the skin, which were graded as absent, mild, moderate, or severe. Patients' self-assessments on whether signs, that could be AEs of GCs on the skin, had ever occurred or had occurred since the beginning of GC therapy, were graded the same way. Only potential AEs graded as moderate or severe were included in the statistical analysis.

Statistical analysis

Summary statistics for continuous, normally distributed data were the mean and standard deviation and for not normally distributed data the median and interquartile range (IQR); between group comparisons were performed with *t*-tests and ANOVA, or Mann-Whitney U-tests and the Kruskal-Wallis-tests, respectively. For categorical data, count and frequency comparisons were done with Fisher's exact tests. Logistic regression was used for analysing continuous GC doses as predictor variables on binary outcomes, *i.e.* the cutaneous AEs. A p-value <0.05 was considered statistically significant. No adjustment for multiple testing was done. IBM SPSS Statistics v. 19 was used for analyses.

Results

In total, 381 RA patients were enrolled, 214 at centre 1 and 167 at centre 2. In Table I, the demographic, disease- and therapy-related data are summarised. With regard to demographic and disease-related data, both samples were similar which allowed us to combine the data for further analyses. However, based on the different recruitment approaches, there were some (expected) differences between the two groups with regard to the distribution of GC doses among the patients. In centre 1, 44 (21%) of the patients had not used GC therapy during the past 12 months. Of the 170 (79%) who had received GCs at least once during the past 12 months, 66 (31%) had been treated with a mean prednisone equivalent dose of <5 mg/d, 88 (41%) received an average dose between 5 and 7.5 mg/d, and 16 (7.5%) were dosed at >7.5 mg/d. Patients from centre 2 were selected by their GC dose, which resulted in four approximately equally sized dose groups, with 40–43 patients each.

Prednis(ol)one was the most commonly used GC in both centres (90%). The number of patients who had received a short course of high dose GC (doses >50 mg/d prednisone equivalent) during the last 12 months was similar between the 2 centres. The mean (SD) total duration of GC therapy was 6.4 (6.9) years, and the mean total cumulative GC dose was 14 (17) g. Patients from centre 2 as compared to those from centre 1 had a higher mean DAS28 (3.3 (1.4) *vs.* 2.6 (1.2), p<0.001) and had received a higher number of different conventional DMARDs in the past (3 *vs.* 2.2, p<0.001). There was no significant difference in the number of different previously received biological DMARDs (bDMARD).

With increasing dose categories of actual GC use, significantly more patients reported Cushingoid habitus, easy bruising, skin atrophy, and impaired wound healing (p<0.001 for all AEs) (see Fig. 1). In the highest dose category, Cushingoid habitus was reported by 38%, easy bruising by 36%, skin atrophy by 41%, and impaired wound healing by 29% of patients, while these were less frequently reported by patients without GC use: Cushingoid habitus by 10%, easy bruising by 6.7%, skin atrophy by 6%, and impaired wound healing by 5.6%. At targeted physical examination, only Cushingoid habitus (p<0.001) was detected more frequently with increasing GC dose categories, and ecchymosis numerically, though not statistically significantly, probably due to the small number of events. At targeted physical examination, Cushingoid habitus was found in 38% and ecchymosis in 10% of the patients in the highest GC dose category, and only in 1.1% and 3.3%, respectively, of the patients without GC use, see Supplementary Tables I and II online at *www.clinexprheumatol*.org.

There was no significant correlation between GC use and the occurrence of abnormal stretch marks, acne, perioral dermatitis, hirsutism and thinning of scalp hair/alopecia.

Influence of comorbidity and co-medication

Diabetes mellitus did not have a statistically significant effect on wound healing (p=0.42), but taking aspirin increased the prevalence of ecchymosis (p=0.014) and easy bruising (p=0.006). Patients without GC therapy had a 2.4 higher risk of ecchymosis and a 2.95 higher risk of easy bruising when taking aspirin. In addition, GC usage also increased the prevalences of easy bruising (p<0.001) and of ecchymosis; the latter only numerically, not statistically significantly, as described above. In contrast, usage of NSAIDs and vitamin-K antagonists had no significant influence on ecchymosis and easy bruising.

Centre effect in cutaneous AEs

Higher rates of Cushingoid habitus were found in centre 1 by both patients' self-assessment and clinical examination in all four dose categories (all p<0.01). In the two highest dose categories, this centre effect was the strongest. Furthermore, there were centre differences for easy bruising and ecchymosis in the dose group <5 mg (p<0.01), and for hair thinning in the dose groups <5 mg and 5–7.5 mg (all p<0.05).

Table I. Demographic, disease, and therapy distributions of the patient cohorts.

Demographic characteristics	Centre 1	Centre 2	all
Number of patients	214	167	381
Female patients (%)	79.4	70.7	75.6
Age in years (mean (SD))	58.4 (13.4)	58.2 (13.7)	58.3 (13.5)
Length in cm (mean (SD))	167 (8.9)	170 (9.5)	168 (9.3)
Weight in kg (mean (SD))	73.5 (16.7)	74.8 (16.1)	74 (16.4)
BMI in kg/m^2 (mean (SD))	26.4 (5.7)	25.8 (5.2)	26.1 (5.5)
Obesity (BMI > 25 kg/m^2) (in %)	33	15	25
Diabetes mellitus (%)	12.6	9.0	11.0
Past pregnancies (% of total women)	75	75	75
Patients (%) with comedication with aspirin/ NSAID/Vit K antagonist	11/27/6	13/41/4	12/33/5
No GC use group	8/11/2	9/46/2	9/28/2
<5 mg/d group	15/19/6	10/41/2	13/28/4
5 – 7.5 mg/d group	12/35/8	19/36/10	14/35/9
>7.5 mg/d group	5/53/5	13/44/0	10/47/2
Disease-related characteristics	**Centre 1**	**Centre 2**	**all**
Disease duration in years (median [IQR])	8 [4;15]	10 [4;20]	9 [4;17]
DAS28-CRP (mean (SD))	2.6 (1.2)	3.3 (1.4)	2.9 (1.3)
Global functional status (ACR 1991 revised criteria) (n (%))			
Class 1	118 (55.1)	88 (52.7)	206 (54.1)
Class 2	75 (35.0)	66 (39.5)	141 (37.0)
Class 3	21 (9.8)	13 (7.8)	34 (8.9)
Class 4	0	0	0
Rheumatoid factor positive (%)	66.4	67.1	66.7
ACPA positive (%)	63.6	59.6	61.9
Erosive disease (%)	54.7	51.5	53.3
Therapy-related characteristics	**Centre 1**	**Centre 2**	**all**
Number of DMARDs used (mean)	2.2	3	2.6
None (n (%))	4 (1.9)	2 (1.2)	6 (1.6)
1	58 (27.1)	28 (17.1)	86 (22.8)
2	74 (34.6)	38 (23.2)	112 (29.6)
3	51 (23.8)	46 (28.0)	97 (25.7)
≥4	27 (12.6)	50 (14.0)	77 (10.3
Number of biologicals used (mean)	1.0	0.9	1.0
None (n (%))	104 (48.6)	87 (52.7)	191 (50.4)
1	55 (25.7)	41 (24.8)	96 (25.3)
2	26 (12.1)	15 (9.1)	41 (10.8)
3	17 (7.9)	14 (8.5)	31 (8.2)
≥4	12 (5.6)	8 (4.8)	20 (5.3)
Patients with GC therapy during 12 months before the visit (n (%))	170 (79.4)	124 (74.2)	294 (77.2)
no GC use	44 (20.6)	43 (25.7)	87 (22.8)
< 5 mg/d	66 (30.8)	42 (25.1)	108 (28.3)
5 – 7.5 mg/d	88 (41.1)	42 (25.1)	130 (34.1)
> 7.5 mg/d prednisone equivalent	16 (7.5)	40 (24.0)	56 (14.7)
Patients with pulse-therapy (GC > 50 mg/d) at least once during 12 month before the visit (%)	29.0	23.4	26.5
Life-time total GC dose in g (mean (SD))	13.7 (16.8)	10.6 (16.5)	12.4 (16.7)
no GC use	3.0 (4.3)	0.2 (0.7)	1.6 (3.4)
< 5 mg/d	13.8 (18.6)	5.4 (7.2)	10.1 (15.2)
5 – 7.5 mg/d	16.5 (15.8)	15.1 (16.7)	16.1 (16.0)
> 7.5 mg/d prednisone equivalent	25.2 (22.2)	23.2 (22.2)	23.9 (22.0)
Total duration of GC use in years (median [IQR])	4.9 [1.8; 9.3]	1.5 [0.0;7.0]	3.0 [1.0;9.0]
no GC use	0.4 [0.0;2.0]	[0.0;0.0]	[0.0;0.8]
< 5 mg/d	6.6 [3.3;10.5]	1.5 [1.0;4.0]	3.5 [1.5;9.0]
5 – 7.5 mg/d	7.3 [2.5; 11.0]	6.0 [1.5;11.0]	7.0 [2.0;11.0]
> 7.5 mg/d prednisone equivalent	5.0 [2.3; 12.0]	4.0 [1.0;11.0]	4.0 [2.0;11.0]

GC: glucocorticoid; ACR: American College of Rheumatology; ACPA: anti-citrullinated protein-peptide antibodies; BMI: body mass index; CRP: C-reactive protein; DAS28: 28 joint disease activity score; DMARD: disease-modifying anti-rheumatic drug; NSAID: non-steroidal anti-inflammatory drug; SD: standard deviation; IQR: interquartile range

Life long cumulative dose and cutaneous AEs

The increase in risk for AEs was calculated for 1000 mg steps. A positive correlation between signs and cumulative GC dose was observed by patients' self-assessments for Cushingoid habitus, easy bruising, skin atrophy, and impaired wound healing; at univariate logistic regression analyses odds ratios (OR) (95% CI) were 1.028 (1.01–1.044), 1.034 (1.016–1.053), 1.134 (1.091–1.178) and, 1.022 (1.008–1.036), respectively, all $p<0.001$.

The physical examination data revealed positive correlations for Cushingoid habitus and ecchymosis only, with OR (95% CI) of 1.019 (1.005-1.032) and 1.013 (1.000–1.027), respectively, both $p<0.001$. No correlations between cumulative dose and abnormal stretch marks, acne, perioral dermatitis, hirsutism, and thinning of scalp hair/alopecia were observed.

Discussion

In total 381 RA patients were examined at both centres. To end up with four large enough dose groups, but also to be able to compare the distribution of GC intake of consecutive standard care patients with that of previous studies, different recruitment methods were applied in each centre.

With regard to demographic and disease-related characteristics, the combined data from both centres were similar to those of the national database (NDB) of the German Collaborative Arthritis Centers (20). The NDB provides information about demographic characteristics, diagnosis, treatment, and clinical status of patients with rheumatic diseases in Germany and represents healthcare in German rheumatology as a whole. Thus, our patient data were representative for patients suffering from RA in general.

Our results indicate that dose and duration of GC therapy determine the pattern and frequency of AEs on the skin. Cushingoid habitus, easy bruising, skin atrophy, impairment of wound healing and ecchymosis were associated with increasing daily as well as cumulative GC doses. A hypothetical explanation for the lack of correlation of acne and

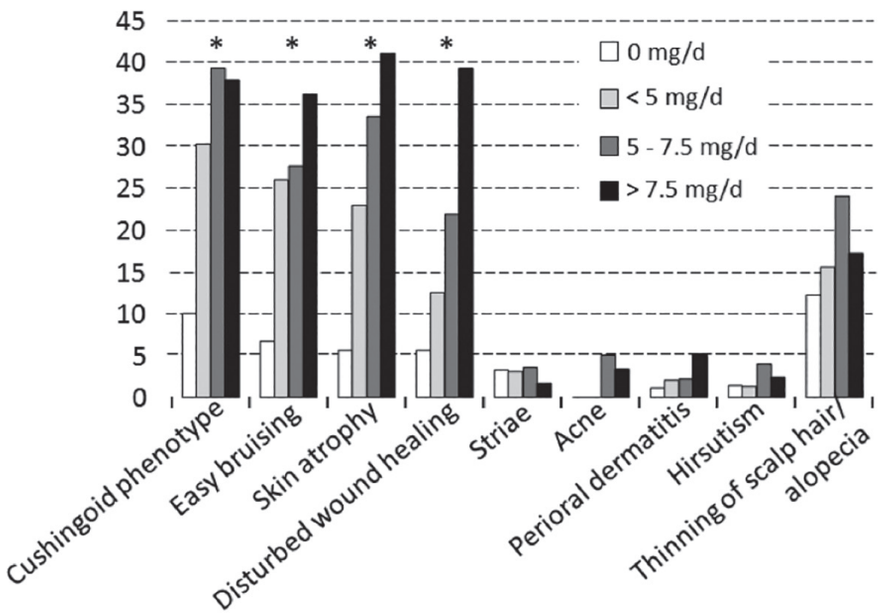

Fig. 1. Patients' assessments of cutaneous adverse effects.
*indicates statistically significant association (p<0.001) between glucocorticoid dose and prevalence of this adverse-effect.
No centre effects for these adverse-effects, with the exception of thinning of scalp hair/alopecia, of which the scored prevalence was higher in centre 1.

perioral dermatitis with cumulative GC dose could be that the nature of these AEs is inflammatory, due to a disturbed balance between pro- and anti-inflammatory cytokines induced by GC. Therefore, a more rapid reversibility of these AEs could occur as compared to AEs on the skin induced by rather metabolic GC effects, such as Cushingoid appearance. In agreement with our data, previous observations showed a linear increase in Cushingoid habitus, ecchymosis and parchment-like skin with increasing GC doses (21). Remarkably, in this previous study and in the present study, these AEs were found even at low-dose GC therapy, *i.e.* ≤7.5 mg/d of prednisone equivalent (22), formerly referred to as the "Cushing threshold". In the lowest GC dose category (<5 mg/d prednisone equivalent), Cushingoid habitus, easy bruising, skin atrophy and impairment of wound healing were assessed approximately 2–3 times as often as in the no GC category. GCs have a catabolic effect on keratinocytes and fibroblasts and decrease vascular structural integrity, which are thought to be the mechanisms of AEs on the skin (23). Apparently, even very low GC doses can drive these mechanisms.

We observed low frequencies of abnormal stretch marks, acne, perioral dermatitis, thinning of scalp hair/alopecia, and hirsutism in our study, and these were not correlated with GC therapy.

Limitations of our study include its cross-sectional design and relatively small numbers of cases, particularly in the GC dose category >7.5 mg/d, probably because current treatment recommendations suggest avoiding higher than daily low dosages, if possible. Although we aimed for an objective method for assessment of Cushingoid habitus, clearly higher rates were documented in centre 1 (both by patient assessment and clinical examination). Its assessment is subjective and probably influenced by cultural background and individual factors (age and body fat). Indeed, the patients in centre 1 clearly were more overweight than those in centre 2. Nevertheless, in both centres, a positive correlation between the GC dose, even in the low-dose range, and Cushingoid habitus was present. We also observed a centre effect for thinning of scalp hair/alopecia in the dose groups <5 mg and 5–7.5 mg (both by patient assessment and clinical examination) with more cases in centre 1. However, even when analysed separately, there was no significant correlation between GC dose and thinning of scalp hair/alopecia in either centre. The centre differences for easy bruising and ecchymosis in the dose group <5 mg revealed by statistically analysis can be explained by small case numbers in our study.

The strength of this study is that it systematically quantified signs that could be AEs of GCs on the skin in a population, which is similar to a generic RA-population. Results therefore are broadly generalisable. Furthermore, the study applied a control group (*i.e.* patients not using or having used GCs).

Conclusion

At lower GC doses, the risk for abnormal stretch marks, acne, perioral dermatitis, thinning of scalp hair/alopecia, and hirsutism is not increased. However, Cushingoid habitus, easy bruising, ecchymosis, skin atrophy and impairment of wound healing occur even at GC dosages <5/mg prednisone equivalent, indicating there is no safe GC dose threshold for certain AEs on the skin.

Key messages

- There is no safe glucocorticoid dose threshold regarding certain adverse effects on the skin
- Even at low-dose chronic glucocorticoid use, skin atrophy and Cushingoid habitus frequently occur.
- At low-to-medium doses, stretch marks, acne, perioral dermatitis, thinning of scalp hair/alopecia, and hirsutism were infrequent.

References

1. FARDET L, PETERSEN I, NAZARETH I: Prevalence of long-term oral glucocorticoid prescriptions in UK over the past 20 years. *Rheumatology* (Oxford) 2011; 50: 1982-90.
2. OVERMAN RA, YEH JY, DEAL CL: Prevalence of oral glucocorticoid usage in the United States: a general population perspective. *Arthritis Care Res* (Hoboken) 2013; 65: 294-8.
3. BIJLSMA JW, JACOBS JW, BUTTGEREIT F: Glucocorticoids in the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2015; 33 (Suppl. 92): S34-36.
4. CALABRO A, CATERINO AL, ELEFANTE E *et al*.: One year in review 2016: novelties in the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2016; 34: 357-72.
5. BUTTGEREIT F: Do the treatment with glucocorticoids and/or the disease itself drive the impairment in glucose metabolism in patients with rheumatoid arthritis? *Ann Rheum Dis* 2011; 70: 1881-3.

6. NEOVIUS M, SIMARD JF, ASKLING J: Nationwide prevalence of rheumatoid arthritis and penetration of disease-modifying drugs in Sweden. *Ann Rheum Dis* 2011; 70: 624-9.
7. VAN DER GOES MC, JACOBS JW, BOERS M *et al*.: Patient and rheumatologist perspectives on glucocorticoids: an exercise to improve the implementation of the European League Against Rheumatism (EULAR) recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2010; 69: 1015-21.
8. DURU N, VAN DER GOES MC, JACOBS JW *et al*.: EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2013; 72: 1905-13.
9. DA SILVA JAP, JACOBS JWG, KIRWAN JR *et al*.: Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. *Ann Rheum Dis* 2006; 65: 285-93.
10. HOES JN, JACOBS JW, VERSTAPPEN SM, BIJLSMA JW, VAN DER HEIJDEN GJ: Adverse events of low-to-medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. *Ann Rheum Dis* 2009; 68: 1833-8.
11. VAN DER GOES, JACOBS JWG, BOERS M *et al*.: Monitoring adverse events of low-dose glucocorticoids therapy: EULAR recommendations for clinical trials and daily practice. *Ann Rheum Dis* 2010; 69: 1913-9.
12. DOSHI A, ZAHEER A, STILLER MJ: A comparison of current acne grading systems and proposal of a novel system. *Int J Dermatol* 1997; 36: 416-8.
13. HAMILTON JB: Patterned loss of hair in man; types and incidence. *Ann N Y Acad Sci* 1951; 53: 708-28.
14. NORWOOD OT: Male pattern baldness: classification and incidence. *South Med J* 1975; 68: 1359-65.
15. LUDWIG E: Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. *Br J Dermatol* 1977; 97: 247-54.
16. WOLLENBERG A, BIEBER T, DIRSCHKA T *et al*.: Perioral dermatitis. *J Dtsch Dermatol Ges* 2011; 9: 422-7.
17. WOLLENBERG A, OPPEL T: Scoring of skin lesions with the perioral dermatitis severity index (PODSI). *Acta Derm Venereol* 2006; 86: 251-2.
18. YILDIZ BO, BOLOUR S, WOODS K, MOORE A, AZZIZ R: Visually scoring hirsutism. *Hum Reprod Update* 2010; 16: 51-64.
19. FERRIMAN D, GALLWEY JD: Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab* 1961; 21: 1440-7.
20. ZIEGLER S, HUSCHER D, KARBERG K *et al*.: Trends in treatment and outcomes of rheumatoid arthritis in Germany 1997-2007: results from the National Database of the German Collaborative Arthritis Centres. *Ann Rheum Dis* 2010; 69: 1803-8.
21. HUSCHER D, THIELE K, GROMNICA-IHLE E *et al*.: Dose-related patterns of glucocorticoid-induced side effects. *Ann Rheum Dis* 2009; 68: 1119-24.
22. BUTTGEREIT F, DA SILVA JA, BOERS M *et al*.: Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. *Ann Rheum Dis* 2002; 61: 718-22.
23. DAVIS GF: Adverse effects of corticosteroids: II. Systemic. *Clin Dermatol* 1986; 4: 161-9.