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The Association between Systemic Glucocorticoid use and the Risk of Cutaneous Adverse Events in patients with Rheumatoid Arthritis: A Systematic Review

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The Association between Systemic Glucocorticoid use and the Risk of Cutaneous Adverse Events in patients with Rheumatoid Arthritis: A Systematic Review

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ABSTRACT

Objectives: Systemic glucocorticoids are used to treat rheumatoid arthritis despite their side effects. There is in literature data concerning risk of glucocorticoid adverse events, however, no definite conclusions can be drawn, especially when it comes to cutaneous adverse events. The aim of this systematic review of the literature was to determine the association between systemic glucocorticoid use and the risk of cutaneous adverse events in rheumatoid arthritis.

Methods: A systematic review of the literature was carried out using PubMed and MEDLINE. All randomized clinical trials comparing glucocorticoids use to non-use in rheumatoid arthritis populations were sought. Data extraction was performed by a single reviewer including incidence of cutaneous adverse effects in each arm, dose and duration of therapy.

Results: Fifteen randomized clinical trials met eligibility criteria, however only five reported cutaneous adverse events, suggesting significant under-reporting. The cutaneous adverse events reported were: alopecia, cushing's syndrome, hypertrichosis, striae, bruising, skin thinning, dermatitis, exanthema, petechiae, leg ulcers and skin infections. Comparison of the two groups – glucocorticoid exposure and non-exposure during a maximum of two years follow-up – revealed a similar number of cutaneous adverse events.

Conclusions: This systematic review revealed that the risk of developing cutaneous adverse events with glucocorticoids is mild and similar between the exposed and non-exposed group. However, the evidence is weak and scarce, and the safety profile of glucocorticoids remains elusive. Therefore, these findings revealed an emergent need of performing randomized clinical trials specifically designed to evaluate adverse events with standardized methods of monitoring and reporting.

Keywords: Rheumatoid Arthritis, Adverse Events, Glucocorticoids, Cutaneous.

RESUMO

Objetivos: Os glucocorticoides orais sistémicos são utilizados no tratamento da artrite reumatóide, apesar dos seus efeitos adversos. Existe informação na literatura sobre os efeitos adversos dos glucocorticoides, no entanto, não se podem tirar conclusões definitivas, especialmente no que respeita os efeitos adversos cutâneos.

O objetivo desta revisão sistemática foi determinar a relação entre o uso de glucocorticoides orais sistémicos e o risco de efeitos adversos cutâneos em doentes com artrite reumatóide.

Métodos: Uma revisão sistemática da literatura foi conduzida com recurso às bases de dados PubMed e MEDLINE. Todos os ensaios clínicos randomizados que comparavam doentes expostos a glucocorticoides com doentes não expostos foram pesquisados. A Um revisor independente fez a extração da informação dos estudos e extraiu informação relativa aos dados da incidência/prevalência dos efeitos adversos cutâneos em cada braço do estudo, doses e duração da terapia.

Resultados: Quinze estudos clínicos randomizados cumpriram os critérios de elegibilidade. Destes, apenas cinco estudos descreveram efeitos adversos cutâneos, sugerindo um baixo número de efeitos adversos reportados. Os efeitos adversos cutâneos reportados foram: alopecia, síndrome de Cushing, hipertricose, estrias, hematomas, atrofia cutânea, dermatite, exantema, petéquias, úlcera do membro inferior e infeções dermatológicas. A comparação entre os grupos expostos e não expostos aos glucocorticoides revelou um número equivalente de efeitos adversos cutâneos nos dois grupos.

Conclusões: Esta revisão sistemática mostrou que o risco de desenvolver efeitos adversos cutâneos na artrite reumatoide é baixo e equivalente entre o grupo dos expostos e não expostos aos glucocorticoides. No entanto, a evidência é fraca e escassa, e o perfil de segurança dos glucocorticoides mantém-se incerto. Assim, os resultados desta revisão demonstraram a necessidade emergente da realização de estudos clínicos randomizados especificamente desenhados para avaliar os efeitos cutâneos adversos utilizando métodos protocolizados protocolados de monitorização.

Palavras Chave: Artrite Reumatóide, Efeitos Adversos, Glucocorticoides, Pele.

LIST OF ABREVIATIONS

BARFOT	Better Anti-rheumatic Farmacotherapy
CAMERA	Computer Assisted Management in Early Rheumatoid Arthritis
DMARD	Disease-Modifying Antirheumatic Drug
EULAR	European League Against Rheumatism
GLORIA	Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis
IM	Intramuscular
LDPT	Low Dose Prednisolone Therapy
MTX	Methotrexate
NSAID	Nonsteroidal anti-inflammatory drug
SSZ	Sulfasalazine

INDEX

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic, chronic inflammatory disease, which entails cartilage and bone damage as well as disability and decreased quality of life (1). Approximately 0.5-1.0% of the world population is affected by RA, with an incidence of 5-50 per 100 000 new cases annually(2)

Current treatment strategies have considerably improved the prognosis (1). One of the treatments responsible for that is Glucocorticoids (GC), which exhibit anti-inflammatory and immunosuppressive properties(1). GCs were demonstrated to allow a better symptomatic control and have disease-modifying properties (3)**.** Namely, studies have revealed that the use of low-dose GC slows the radiographic progression of articular disease, especially in early RA (4). Surveys reveal that at any given time, 30 to 80% of RA patients will be on low-dose GCs. Clinical trial data show that about 50 percent of RA patients included in trials are on GCs.

Despite the crucial role of GCs in RA treatment, the fear of adverse AEs resulted in loss of confidence in GCs by both physicians and patients and restrained its use (4,5). Several reports exist on the AEs of GCs, however, no definite conclusions can be drawn, because most of the data comes from observational studies, with the inherent risk of bias (5). Hence, in present days, there is still an ongoing debate about the balance between the benefit and harm of GC treatment (1). An example is that North American publications tend to underscore the risks, whereas many European researchers argue that the toxicity of low-dose GC therapy in RA is frequently overestimated, while its benefits are downplayed (6).

Evidence regarding GC cutaneous-AEs are often conveyed by observational studies (1,7,8) with low levels of quality. Observational studies provide in general weak evidence since, due to the lack of randomization, they are inherently affected by indication bias and other methodological issues that hinder interpretation. Such strong bias cannot be overcome by statistical techniques(6,9). We need to consider the possibility that at least some of the AE attributed to GC in observational studies are in fact due to concomitant medications or to the disease itself. In clinical practice, as reflected by observational studies, patients with more severe disease are more frequently prescribed GC at higher doses and more intense comedication, which can obviously increase the risk of unwanted events that will be falsely attributed to GCs, instead of the disease itself, comorbidities and/or comedication(6).

Literature reveals that observational studies show higher rates of AE than the randomized prospective studies, especially regarding infection. On the other hand, pertinent

RCTs conducted in Europe concluded that the use of low-dose GC in RA is associated with mild toxicity (6).

However, RCTs have limitations of their own. The difficulty is that most of the studies had been designed to assess treatment effects and not GC-AEs. Additionally, the recommendations and research agenda from EULAR (10) is relatively recent information, and before that, studies were lacking some important monitorization. This paper aimed to develop recommendations on monitoring for adverse events (AEs) of low-dose glucocorticoid (GC) therapy (≤7.5 mg prednisone or equivalent daily) in clinical trials and daily practice. The three main recommendations of EULAR were to: report all monitoring results of trials; to report both on the group level (eg, means) and on the individual patient level (eg, numbers); to develop new tools for assessing specific adverse events(10).Clinical trials large enough to evaluate the long-term balance of benefit and harm of low-dose GCs are lacking (1). Other major problem is the lack of a validated method to clinically and objectively monitor and evaluate AEs (11), which can lead to heterogenous results between studies. The methods used were checklists along with follow-up visits and spontaneous reports (1).

Overall, there is a lack of good quality evidence, information is scattered, fragmented and disperse which raises the need of performing a systematic review including randomized clinical trials (RCTs), which provide the best evidence. Therefore, the aim of this systematic literature review is to examine the association between the use of low- and medium-doses of systemic GC and the risk of cutaneous AEs in patients with RA, attempting to create a valid AEs profile of GC therapy, in accordance with EULAR recommendations (10).

MATERIALS AND METHODS

Search Strategy

A systematic review of the literature was carried out in PubMed and MEDLINE databases, looking for randomized controlled trials (RCTs) published between January 2000 and September 2019. The search strategies included free terms and medical descriptors (eg, MeSH terms) for each PICO synonym. Some terms used were: “rheumatoid arthritis”, “glucocorticoids”, “cutaneous”, “adverse events”. Also search through references was made.

Eligibility criteria

Only studies fulfilling the following inclusion criteria were selected for detailed analysis: (1) RCTs; (2) including adults diagnosed with RA; (3) treated with systemic GC therapy (oral, intramuscular or intravenous) in one arm and non-exposure (no treatment or placebo) in at least one comparator arm; (4) GCs were used in dosages <30mg of prednisone or equivalent daily; (5) studies lasted 6 months or longer; (6) published in European languages (including, English, French, Spanish Italian, Portuguese).

Studies including other population besides RA were excluded. Studies reporting topical, intra-articular or intra-ocular use of GCs were excluded.

Study Selection

Eligibility assessment was performed independently, on the basis of title and abstract, by two authors (IC, ML) and disagreements were discussed with a third author (TS). Later, studies selected for this systematic review were reviewed in full-text.

Data extraction

Data extraction was performed by a single reviewer (IC) using an excel spreadsheet form. Information was extracted regarding: (1) the RA population including age, gender and disease duration; (2) the exposure, including the definition of GC (prednisone or prednisolone) use, dose and duration of therapy; (3) the comparator arm including whether this was placebo or non-GC exposure (4) the outcome of cutaneous AEs in each arm; (5) how cutaneous AEs were monitored; (6) and statistical results of cutaneous AEs in both arms of prednisolone group and control group.

RESULTS

A total of 105 articles were identified from PubMed, MEDLINE from citation search. After removing duplicates, 67 RCTs were screened by title and abstract review, and a final total of 15 RCTs were included after applying eligibility criteria. Of the 15 RCTs selected, only 5 reported on cutaneous AEs (Figure 1) We cannot acknowledge if the other studies didn't report cutaneous AEs because they didn't monitored cutaneous AEs at all or if they monitored but there were no cutaneous AEs reported.

The 15 RCTs selected for this review are presented in Table 1 in the attachments, with the description of the main features and findings of each trial. Two main groups were compared: group of patients exposed to GCs such as prednisone or prednisolone (Pred-group) and group of patients not exposed to GCs (NoPred-group).

Ten of these RCTs did not describe the method used for monitoring GC-AEs (12–21). One of these RCTs, Pincus T. study (19) did not inform about the method of monitoring but reported cutaneous AEs. Capell et al. (22), Bakker et al. (23), Wassenberg et al. (24), van Everdingen et al. (25), monitored AEs through a checklist. Svensson et al. (26) used follow-up visits and spontaneous reports. The checklists used for the monitorization of AEs were not described in the articles, so we contacted the authors and asked for this information.

In total, 2482 RA patients were enrolled in these trials, of which 1190 were exposed to low-dose and medium dose of GCs (≤10 mg of prednisone or equivalent a day). Of the studies that reported cutaneous AEs, a total of 60 RA patients of the Pred-group developed cutaneous AEs and 73 on the NoPred-group, over a follow-up up two years. Below we describe, the five RCTs that reported cutaneous AEs. The first four RCTs used a checklist for monitoring AEs. (Table 1 in Appendix I).

In CAMERA II (Computer Assisted Management in Early Rheumatoid Arthritis trial-II) (23), Bakker et al. monitored GC-AEs over 2 years through a standard checklist of AEs known to be related with prednisone, at every study visit. Over the 2 years period study, 17% of the patients of Pred-group reported cutaneous AEs compared with 23,5% in the NoPred-group. Alopecia was one of the events resulting in withdrawals from the study (no data was reported regarding the number of withdrawals). Patients who withdrew may have had more than one AE, but no more information was given (23).

In the Pincus study (19), the authors only mentioned bruising and skin thinning as GC-AEs, over one year, but didn´t give any additional information neither the method of reporting AEs.

In the LDPT (Low Dose Prednisolone Therapy) study (24), Wassenberg et al. used a checklist to monitor GC-AEs over the 2 years. The authors reported that 26,9% of the Pred-group reported cutaneous AEs, in comparison with 28% of the NoPred-group. Cushing's syndrome developed in more patients of the Pred-group (5 patients) than in the NoPred-group (0 patients). In this RCT all dropouts due to AEs were attributed to the concomitant treatment with gold or MTX (24).

In the Utrecht study (25) van Everdingen et al., was used a standardized list to record the AEs. Cutaneous AEs (excluding infections) were registered in 15% of the Pred-group and 19.5% of the NoPred-group over 2 years. Cases of skin thinning, or easy bruising were not reported. On the other hand, 5 episodes of erysipela were observed in 4 patients from the NoPred-group differing from the Pred-group which didn't have any episode of erysipela. In this study, except for infections, the two groups had an equal number of adverse effects affecting the skin, which were well controlled with conservative treatment, according to the study (25).

The BARFOT (Better Anti-rheumatic Farmacotherapy) study (26), by Svensson et al. monitored GC-AEs through spontaneous reports by patients or by laboratory values, during 2 years. Cutaneous AEs were registered in 7,4% of the patients of the Pred-group versus 7,7% in the NoPred-group. Ecchymoses were also reported as GC-AEs in this trial, but no more information was given. The frequency of AEs was small in both groups, which means that prednisolone was generally well tolerated (26). According to Svensson et al., prednisolone was judged to be the cause of two withdrawals in the Pred-group; these two patients withdrew (temporary or permanently) due to striae with ecchymoses and cushingoid appearance. The remaining withdrawals (seventeen) were caused by DMARDs (26).

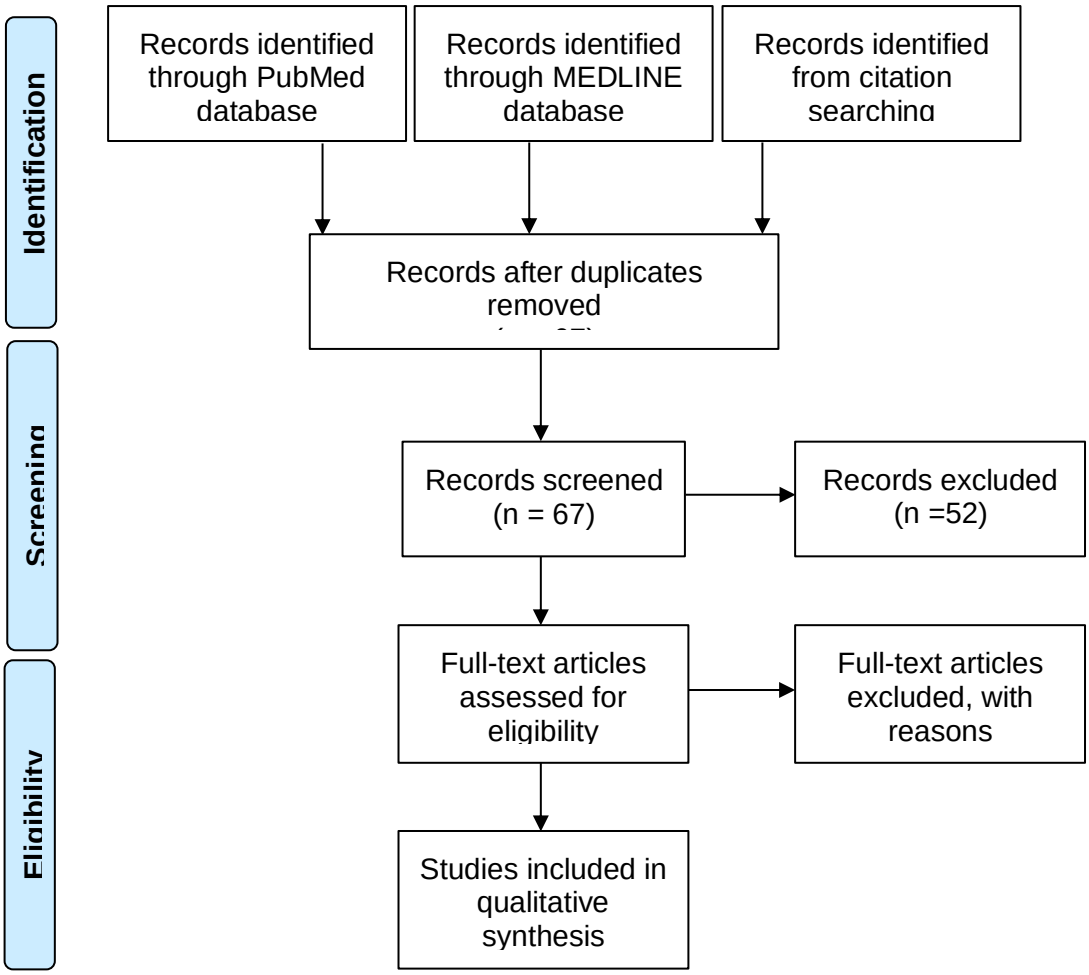

Figure 1- Flowchart of study selection for this systematic review of the literature.

DISCUSSION

This systematic review of the literature revealed that the risk of developing cutaneous GC-AEs in RA patients taking systemic low- and medium- doses of GC (Pred-group) is mild, and barely different from the control group (NoPred-group). The cutaneous AEs reported on the RCTs included were: alopecia (23,24,26), itching (23,24)**,** cushing's syndrome (24,26), hypertrichosis (26), rash (26), striae (26), ecchymoses (26) , bruising (19), skin thinning (19), dermatitis (24), exanthema (24,25), leg ulcer (25)**,** petechiae (25) and skin infections (erysipela) (25). In fact, the NoPred-group revealed slightly higher percentages of cutaneous AEs. Nevertheless, we highlight that information conveyed by the RCTs is very scarce and weak.

The authors emphasize that the RCTs included in this systematic review were designed to assess efficacy after one or two years of GC treatment. They were not specifically designed or powered to establish an association between GC and AEs, so monitoring and reporting of AEs was often limited which leads to highly variable conclusions. Follow-up visits and spontaneous reports by patients were used in order to monitor AEs, however few cutaneous AEs were reported in these studies.

According to Da Silva et al., although most of the cutaneous AEs are not considered serious by the physician, they may represent an important cosmetic problem and be of great concern for the patient (5). Hence, once again we emphasize the importance of studying GC cutaneous AEs. Also, many AEs that are considered important to patients are often difficult to assess and quantify, as, for example, easy bruising or skin athrophy (27). Therefore, monitoring and reporting methods should be meticuslously chosen and this topic should also be adressed on the reasearch agenda.

One of the difficult in these RCTs is that lack of standardized and incomplete conclusions about the development of these AEs (28). In a near future, imaging techniques, such as high-frequency ultrasound and optical coherence tomography may be useful for evaluating dermal and epidermal involvement, respectively (29).

The authors emphasize that the nomenclature of the cutaneous AEs was not standardized. For example, "itching" and "exanthema" or "ecchymoses" and "bruising" have a similar meaning. Between different studies, different nomenclature for skin events was used which difficult the interpretation of studies' results. Hence, we think that cutaneous AEs monitorization would benefit with a multidisciplinary approach between Rheumatology and

Dermatology, in order to have standardized nomenclature and accurate monitoring methods (eg. global acne grading system, Ludwig scale). In fact, the RCTs included in this review, probably performed more methods of monitoring than the ones reported (and access to these results would be important). One example is the Pincus T. study (19) that reported bruising and skin thinning but does not mention the method of monitoring and didn't provide statistical data about the AEs.

One important reflection to take in account is that the low number of studies included (only 5 reporting cutaneous AEs) alongside their small samples sizes reduce the power of the review and can over-estimate or under-estimate the magnitude of the association between GCs and the risk of cutaneous AEs (28). With regard to demographics and disease, it is important to bear in mind that patients who participate on these RCTs may not have the same disease characteristics or comorbidities as patients treated in the real practice, and this should also be considered in future RCTs (5).

The prevalence of RA is expected to increase in Europe over the future years along with the ageing of the population (1) and this population is challenging due to their co-morbidities, co-medication and frailty that increase the chances of AEs (1). We highlight that an important RCT in progress is Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis (GLORIA) Trial (1). This trial is focused on the elderly (patients 65 years of age and older) and its design has harm as co-primary outcome and it is also tailored to address potential confounding factors such as concurrent anti-rheumatic treatments (1). In this study, the authors defined GC *harm* as patients with at least one serious AE or an AE defined as of "special interest". For this purpose, they monitor *harm* by spontaneous descriptions of the patient or physician, and by the results of a 53-item symptom list completed by the patients at the beginning and end of the study (1). One important point is that the AEs considered of "special interest" didn't include any specific cutaneous AE.

In our review we only included RCTs, which have high level of evidence, including two arms with GC-exposure and non-exposure allowing comparison of AEs among the two groups. Despite this, trials included concomitant treatments such as DMARDs and others (NSAIDs, analgesics) whose AEs are not systematically accounted for, making it difficult to understand if AEs were triggered by GCs or other treatments. For example, in the BARFOT study (26), DMARDs were judged to be the main cause of patient withdrawals, compared to prednisolone treatment that was well tolerated. In the Wassenberg et al. study, a lower frequency of cutaneous reactions was seen in the prednisolone-group, and it occurred almost exclusively

in gold treated-patients. Consequently, these results may confirm a previously identified protective effect of prednisolone against cutaneous side effects of gold therapy (24).

We acknowledge that the RCTs included had a relatively short duration (~2 years). Thus, this may not give time to develop certain AEs such as acne and hair effects (hirsutism and alopecia). It's general accepted that these effects are more common with long-term treatment, specifically with medium to high doses of GC (5). Thus, these effects would be better evaluated in long-term trials. Taking this into account, a question arises: *are the mild AEs reported explained by the low- and medium-doses or by the short duration of the studies?*

We have demonstrated that there is a gap on evidence regarding cutaneous toxicity of low- and medium-dose of GCs and definite conclusions cannot be drawn. Given the crucial therapeutic value on RA, the benefits-risk balance of GCs should be furthered evaluated. Indeed, it is essential to follow EULAR GC task force recommendations and accomplished systematic studies with adequate design, sample size, duration and standardized methods of monitoring and reporting (28).

So, where is the fear of glucocorticoid cutaneous adverse effects coming from? The truth is that patients and physicians fear may be influenced by results of studies with high doses of GC (5) and these concepts of dose and time of GC treatment regimens should be studied and clarified.

Taken together the findings from observational studies tend to overestimate or underestimate the effects of the GC treatment and are more heterogenous on the estimation of the effects because of several confounding factors and selection bias. For example, we must highlight that patients with high disease active are seen more often by the rheumatologist. Thus, these patients have a higher probability to be included in observational studies if there is a limited time of enrolment, introducing bias to the observational studies being performed (8). Therefore, these studies cannot be trusted per si as a basis for decision-making to provide the most safety and on state of the art treatment, and that is the reason why these studies should be read more carefully than others. (30).

CONCLUSIONS

In conclusion, this systematic review revealed that the risk of developing cutaneous AEs with low and medium doses of GCs is similar to the control group. However, due to weak and scarce evidence, absolute risk of GCs remains unquantified and extrapolation of results is limited.

Lastly, these findings raise concern about an issue of the utmost importance that is: the emergent need of performing studies specifically designed to evaluate GC-AEs with standardized methods of report or systematically register AEs in all future studies. In both cases, studies should be randomized and should systematically register the type of GC, its regimen, treatment duration, cumulative doses and patient-related factors such as gender, age, weight, comorbidity and co-medication (31). The health professionals and patients' beliefs about GCs risks should be informed. These evidence-based findings proved that more robust studies should be made in order to allow an optimized use of GCs, based on rigorous assessment of their risks and benefits.

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APPENDIX I

Table I - Characteristics of the 15 RCTs of low- and medium-dose GC in RA included in this review.

Study	First author and year	Number of RA; RA duration at entry	Number of patient, Pred-group	GC dose (mg/day)	Study duration (years)	Association DMARDs	Method of monitoring AEs	Dermatological/Cutaneous AEs reported (Yes/No)	Results of Dermatological/Cutaneous AEs (Pred-group vs. NoPred-group)
CAMERA II	**Jurgens et al. , 2014**	236 patients with early RA; <1 year	92	10	2	MTX	Information not available	Information not available	
	Jurgens et al. , 2013	236 patients with early RA; <1 year	109	10	2	MTX	Information not available	Information not available	
	van der Goes et al. , 2013	236 Patients with early RA; <1 year	117	10	2	MTX	Information not available	Information not available	
	Bakker et al. , 2012	236 patients with early RA;	117	10	2	MTX	Standard list of AE known to be related	Alopecia	10 patients (8,5%) Pred-group vs. 17 patients (14,3%) NoPred-group

		<1 year					with prednisone.		
								Itching	10 patients (8,5%) Pred-group vs. 11 patients (9,2%) NoPred-group
BARFOT	**Engvall et al. , 2013**	225 patients with early RA; <1year	108	7.5	2	Various	Information not available	Information not available	
	Forslind et al. , 2009	166 patients with early RA; <1 year	82	7.5	2	Various	Information not available	Information not available	
	Hafström et al. , 2007	67 patients with early active RA; <1	34	7.5	2	Various	Information not available	Information not available	
	Svensson et al. , 2005	250 patients with early active RA; <1	119	7.5	2	MTX or SSZ	AE were registered at the follow-up visits and	Alopecia	1 patient (0,8%) Pred-group vs. 0 patients (0%) NoPred-group
								Cushing's Syndrome	1 patient (0,8%) Pred-group vs. 0 patients (0%) NoPred-group

							were either spontaneously reported or revealed by laboratory values	Hypertrichosis	0 patients (0%) Pred-group vs. 1 patient (0,8%) NoPred-group
								Rash	6 patients (5%) Pred-group vs. 9 patients (6,9%) NoPred-group
								Striae	1 patient (0,8%) Pred-group vs. 0 patients (0%) NoPred-group
								Ecchymoses	Information not available.
Montecucco	**Montecucco et al. , 2012**	220 patients with early RA; <1 year	110	6.25	1	MTX	Information not available	Information not available	
Pincus T	**Pincus T, 2011**	31 patients with RA;	15	1-4	1	MTX	Information not available.	Bruising, Skin thinning	Information not available.
Tengstrand B	**Tengstrand B et al. , 2007**	58 patients with RA treated with prednisolone (5–7.5mg) for at least 2 years	30	5-7,5	2	Various	Information not available.	Information not available	
LDPT	**Wassenberg et al. , 2005**	192 patients with early RA; <2 years	93	5	2	IM gold or MTX	Checklist for monitoring AE	Dermatitis	4 patients (4,3%) Predroup vs. 9 patients (9,4%) NoPred-group
								Exanthema	9 patients (9,7%) Pred-group vs. 8 patients (8,3%) NoPred-group

								Alopecia	3 patients (3,2%) Pred-group vs. 8 patients (8,3%) NoPred-group
								Itching	4 patients (4,3%) Pred-group vs. 2 patients (2%) NoPred-group
								Cushing´s syndrome	5 patients (5,4%) Pred-group vs. 0 patients (0%) NoPred-group
WOSERACT	**Capell et al. , 2004**	167 patients with active RA; median 1 year	84	7	2	SSZ	Checklist for measurements of GC toxicity	No cutaneous AEs reported. (AEs related to other systems were reported)	
UTRECHT	**van Everdingen et al., 2004**	81 patients with early RA; <1 year	40	10	2	SSZ rescue	Information not available.	Information not available	
	van Everdingen et al. , 2002	81 patients with early active RA; <1 year	40	10	2	SSZ rescue	Standardized list was used to document AEs.	Leg ulcer	3 patients (7,5%) Pred-group vs. 2 patients (4,9%) NoPred-group
								Exanthema	2 patients (5%) Pred-group vs. 1 patient (2,4%) NoPred-group
								Petechiae	1 patient (2,5%) Pred-group vs. 1 patient (2,4%) NoPred-group
								Skin infections treated with antibiotics	0 patients (0%) Pred-group vs. 4 patients (9,8%) NoPred-group

								(erysipelas)	

Legend:
Pred-group = group of patients exposed to glucocorticoids (prednisone or prednisolone); NoPred-gorup = group of patients not exposed to glucocorticoids; RA = Rheumatoid Arthritis; GC = Glucocorticoid; AE = Adverse Event; MTX = Metotrexate; SSZ = Sulfasalazine; BARFOT= Better Anti-rheumatic Farmacotherapy; CAMERA = Computer Assisted Management in Early Rheumatoid Arthritis; DMARD = Disease-Modifying Antirheumatic Drug; GLORIA = Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis; LDPT = Low Dose Prednisolone Therapy; MTX = Methotrexate; SSZ = Sulfasalazine; IM = intramuscular.

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