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Adverse events of glucocorticoid pulse therapy in inflammatory diseases: a meta-analysis

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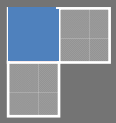

Master thesis information

Title	Adverse events of glucocorticoid pulse therapy in inflammatory diseases: a meta-analysis
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Contents

Abstract

Objective To systematically analyse the literature on reported adverse events of high intravenous pulse glucocorticoids (≥250 mg prednisone equivalent) for inflammatory diseases and transplantation.

Methods A literature search was done using PubMed, Embase, and Cochrane databases. Studies were selected by two reviewers (NAMS and ND). Available data on the prevalence of glucocorticoid-related adverse events (AEs) in patients with RA, systemic sclerosis, asthma, or organ transplantation were retrieved.

Results 50 studies were included, of which 10 studies (451 patients) documented intravenous pulse glucocorticoids-related adverse events. In total, 438 AEs had been recorded, which resulted in an AE rate of 44/100 patient-years. Cardiovascular and infectious adverse events were the most frequent AEs. There were 4 placebo-controlled studies comprising of RA and systemic sclerosis patients, in which the odds ratio of flushing was highest, 14.69 (95% CI 5.34 to 40.46), followed by that of headache: 6.19 (95% CI 2.33 to 16.43). There was also a high risk of lower respiratory tract infection, disturbance of taste, and heart rhythm disorders.

Conclusion: Only relatively few studies are present in the literature that report on intravenous pulse glucocorticoid-related AEs. In RA patients, cardiovascular adverse events are frequently documented, and in systemic sclerosis patients and patient who had transplantation infectious adverse events are predominantly present.

Introduction

Glucocorticoids are hormones that act anti-inflammatory and immunosuppressive(1). In 1949 Hench *et al.* first demonstrated that the steroid hormone cortisone can be used for the treatment of rheumatoid arthritis (RA)(2). Since the Nobel Prize in Medicine was given for this achievement, glucocorticoids have been used in treatment of various inflammatory conditions, such as rheumatoid diseases (RA, temporal arthritis, polymyalgia rheumatica, and systemic lupus erythematosus), obstructive lung diseases (asthma and chronic obstructive pulmonary disease), and inflammatory bowel diseases (ulcerative colitis and Crohn's disease)(3). Glucocorticoids can be given via different routes including intravenous, by inhalation, intramuscular, intra-articular, and oral. The dose and duration of therapy can range from a high dose for short-term to a low dose for long-term therapy. Unfortunately, the occurrence of side effects with daily administration is frequent(4). Therefore, in the 1960s the method intravenous short-term pulse dosing was developed(3). With this, the steroids would still have their beneficial effects but lose adverse events that are associated with daily administration. Despite this method, many adverse events have been reported with intravenous pulse glucocorticoids(5-14).

Previously, Hoes *et al.* described the risk of adverse events of low to medium dose glucocorticoids and a EULAR Task Force formulated recommendations to manage low dose systemic glucocorticoids in daily practice(4). The adverse events caused through low dose glucocorticoids are now better controllable. Though, the risk of adverse events during the administration of medium and high dose glucocorticoids is still unknown.

The aim of this study was to systematically analyse the literature on reported adverse events of medium and high dosages of glucocorticoids and to quantify the risk of adverse events, independent of the underlying inflammatory disease. With this overview recommendations and general guidelines could be developed. The patterns of glucocorticoid therapy are determined as: chronic use (≥ 3 months) of 30 mg or higher (in prednisone equivalent), chronic use (≥ 3 months) of 10-30 mg prednisone equivalent, short term oral use of high doses (≥ 30 mg) with a step down scheme, and intravenous pulse therapy (≥250 mg prednisone equivalent)(15). Here, the adverse events of intravenous pulse therapy will be discussed.

Methods

Literature search

A literature search was performed by NAMS and ND to review glucocorticoid-related adverse events in inflammatory diseases using the bibliographic databases PubMed, Embase and Cochrane Library. The search consisted of relevant keywords for disease, e.g. rheumatoid diseases, obstructive lung diseases, and inflammatory bowel diseases, treatment (medium to high dose glucocorticoids and route of administration), and adverse events which was checked by experts (JWGJ and JWJB). The search terms included keywords, words of the title or abstract, synonyms, and plurals. MESH terms were added for the PubMed search. All search terms were combined using Boolean operators (AND, OR) (see Appendix 1).

Study selection

Studies were selected by two reviewers (NAMS and ND). The studies were included if they applied for the following criteria to the title, abstract, and full text:

- Study population: adults with inflammatory diseases or who underwent transplantation and were treated with glucocorticoids. Patients with other (or no) diseases were excluded.
- Intervention: patients had to receive medium (10-30 mg prednisone equivalent) or high (≥ 30 mg prednisone equivalent) dose glucocorticoids. For intravenous pulse therapy patients had to receive ≥250 mg prednisone equivalent for one or more days. The route of administration had to be intravenous, oral, or intramuscular. If only a part of the total study population received medium or high dose glucocorticoids and their stratified data were reported, this group was included in the analysis. If two or more groups of glucocorticoids were compared and stratified data were reported, these groups were individually analyzed.
- Outcome: number of AE on patients' level caused by glucocorticoid treatment were included.
- Study designs: (randomized) controlled trials, prospective trials, cohort studies, and observational studies were included.

Exclusion criteria were non-English language, animal studies, inhalation of GC, intra-articular administration, glucocorticoids combined with ≥2 other drugs and case reports. Only full text available papers were applied.

Data extraction

The characteristics of included studies were recorded. Relevant characteristics were number of patients, gender, age, type of disease, type and dose of glucocorticoid (medium and high dose), study

duration, patients dropping out from the study (missing data), deaths. The following information about the reported adverse events was collected: type and number of AE, the frequency of monitoring, blinding of investigator, and study methodology (Box 1).

Quality assessment

The selected studies were judged for their quality, using the following criteria (as defined by Hoes *et al.*)(16):

- Predefined AE: Yes; when the study mentioned predefined AE. No; when study did not mention any predefined AE.
- Standardized AE scoring protocol: Yes; the study did use an AE protocol, e.g. questionnaire. No; the study did not use an AE protocol.
- Description of missing data: Yes; when the study gave detail number of missing data and the reason why the data was missing, e.g. drop outs. No; when the study did not mention missing data.

The study could score a quality of 0 to 3 points (1 point per criterion), whereas 3 points was the highest obtainable quality.

Data analysis

Non-pooled adverse events of glucocorticoids versus placebo were analysed using odds ratios. Studies without a placebo group were analysed with events/exposed patients. Analyses were done by using the Comprehensive Meta-Analysis software (Biostat, Engelwood, New Jersey, USA).

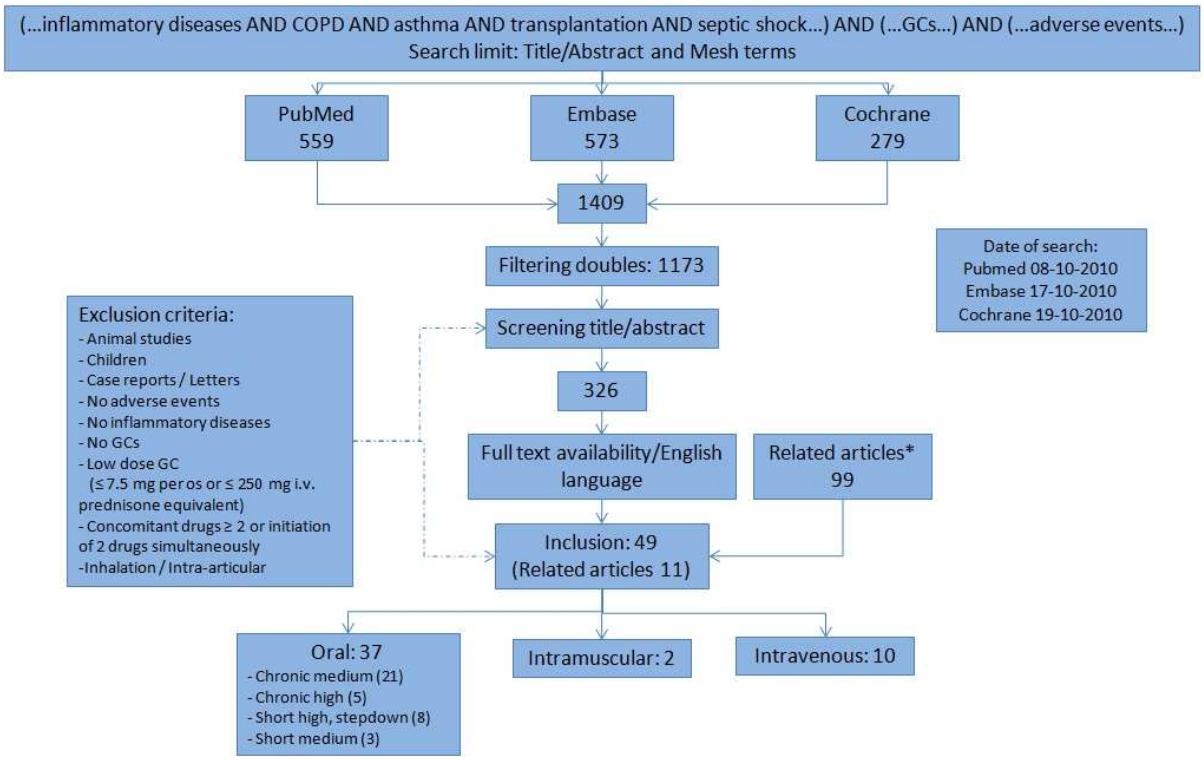
Box 1 Study methodology(16, 17)	
1a	Meta-analysis of randomized controlled trials
1b	Randomized controlled trial
2a	Controlled study without randomization
2b	Quasi-experimental study
3	Descriptive studies (comparative, correlation, case-control)
4	Expert committee reports / opinions and/or clinical opinion of respected authorities

Results

Literature search

Using the specified search strategy (Appendix 1), 1409 studies were obtained, consisting of 559, 573, and 279 hits in PubMed, Embase, and Cochrane, respectively (Figure 1). Doubles were filtered by loading the studies into Reference Manager 11, an electronic bibliographic management system. In total, 236 doubles were deleted. After screening the titles and abstracts, and reading the full texts, 38 articles met the inclusion criteria. Using the reference lists of the full text available studies another 99 studies, related articles, were selected which could be valuable for this study. These articles were screened with the same inclusion criteria and 11 studies were included. In total, 49 articles were included in this study. Ten of the 49 articles discussed intravenous glucocorticoids in rheumatoid arthritis (RA), transplantation (Tx), asthma, and systemic sclerosis (Figure 2). Relevant adverse event (AE) data were extracted from these studies. Only 4 studies compared glucocorticoids with placebo(6-9). The other studies were non-controlled, compared various dosages of glucocorticoids, or compared glucocorticoids with other drugs.

There were studies in which only a part of the study population were included into this study.



*useful articles found in the reference lists of screened articles

Figure 1 Flow chart of the selection of studies. The databases PubMed, Embase, and Cochrane were used to perform the literature search. The obtained articles were screened for doubles. After screening on title and abstract and reading the full text versions, 38 articles were included. From the related articles 11 studies were included. In total, 49 articles met the inclusion criteria, of which 10 articles discussed intravenous glucocorticoids.

For instance, in certain studies two or three groups were compared with different dosages of glucocorticoids, including a dose of <250 mg prednisone equivalent(10, 12), or glucocorticoids were compared in combination with other drugs(11). In two articles, 2 study groups were present(5, 10). These groups were separately analysed.

Adverse events

Adverse events were classified in groups, according da Silva *et al.* (18) and Hoes *et al.* (4) (Box 2). In total, 451 patients received intravenous glucocorticoids and 438 adverse events were recorded, with an AE rate of 44/100 patient-years. Cardiovascular adverse events were most often noted, mainly in RA patients, including heart rhythm disorders, hypertension, and increased diastolic blood pressure. Though, adverse events corrected for the number of exposed patients resulted in the highest occurrence of infectious adverse event (Figure 3). Dermatological, gastrointestinal, and neurological adverse events were only reported in RA patients. Notable is that in patients who had transplantation more infectious and musculoskeletal adverse events were documented. In patients with systemic sclerosis were only infections reported, and one asthma patient suffered from diabetes mellitus. Only Shipley *et al.* recorded a severe adverse event, which was nocturia and increased urinary frequency in a RA patient(10).

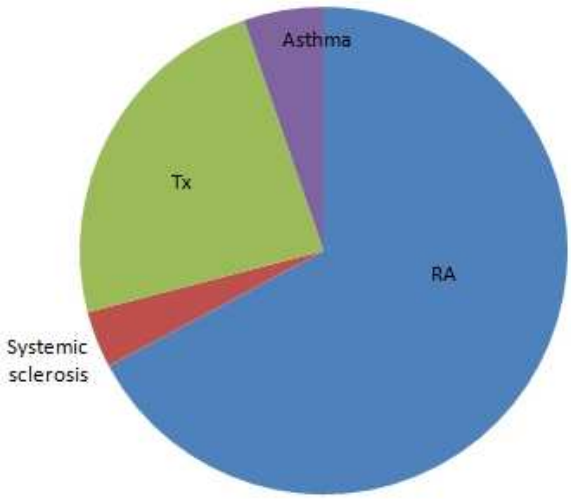


Figure 2 Overview of the study population of the included studies receiving intravenous ≥250 mg prednisone equivalent per day.

Box 2 Glucocorticoid-related adverse events(4)

Musculoskeletal
- Osteoporosis, osteonecrosis, myopathy

Endocrine and metabolic
- Glucose intolerance and diabetes, fat redistribution and body weight, suppression of sex hormone secretion

Cardiovascular
- Dyslipidaemia, atherosclerosis, cardiovascular disease, water and electrolyte balance, oedema, renal and heart function, hypertension

Dermatological
- Cutaneous atrophy, acne, hirsutism, alopecia

Ophthalmological
- Cataract, glaucoma

Gastrointestinal
- Peptic ulcer disease, pancreatitis

Infectious
- Viral, bacterial, skin infections

Psychological and behavioural disturbances
- Steroid psychosis, minor mood disturbances

Neurological
- Headache, vertigo, dizziness, tinnitus

Study characteristics placebo-controlled studies

The study characteristics of the placebo-controlled studies are listed in Table 1. In total, 220 patients received high pulse intravenous glucocorticoids and 218 patients received placebo. Sharada *et al.* reported systemic sclerosis patients who received intravenous dexamethasone. In other studies patients received methylprednisolone and consisted of patients with rheumatoid arthritis. The mean quality of reporting adverse events of these groups was 2 and the length of the study ranged from 3 months to 4.5 years approximately. The majority of studies were randomised double-blinded controlled trials, except for Williams 1988 *et al.* which was a non-randomised controlled trial. Williams 1988 *et al.* reported many various adverse events, while Hansen *et al.* reported high numbers per adverse event, though the study population of Hansen *et al.* was approximately an half smaller.

Odds ratios in placebo-controlled studies

The overall odds ratio of the reported adverse events in the placebo-controlled studies was 1.83 with an at random 95% confidence interval (CI) of 0.98 to 3.40 (p-value 0.06). Most of the adverse events were not significant, except for flushing, heart rhythm disorder, disturbance of taste, lower respiratory infection, and headache (Table 2). The odds ratios showed an increased risk in obtaining these adverse events when intravenous glucocorticoids were administered. Patients recording flushing as an AE had the highest odds ratio of 14.69 (95% CI 5.34 to 40.46), followed by headache with an odds ratio of 6.19 (95% CI 2.33 to 16.43).

Adverse events of nonplacebo-controlled studies

In total, 6 nonplacebo-controlled studies were included in this study. Three studies consisted of patients with rheumatoid arthritis, 2 studies of patients who underwent transplantation, and 1 study with asthma patients. In these studies, 46 various adverse events were documented. In total, 231 patients received intravenous pulse glucocorticoids. A top 20 of the most reported adverse events is listed in Table 3. Increased diastolic blood pressure had the highest event rate, namely 88%. Though, increased diastolic blood pressure was only reported in one study group. Diabetes mellitus was reported in 4 study groups, and osteonecrosis and osteoporosis in 3 study groups, but their event rates were lower, 24.1%, 21.1%, and 18.2%, respectively. An extensive overview of intravenous administered glucocorticoid-related adverse events in nonplacebo-controlled studies, including the event rate (event/exposed patients), is shown in Appendix 2.

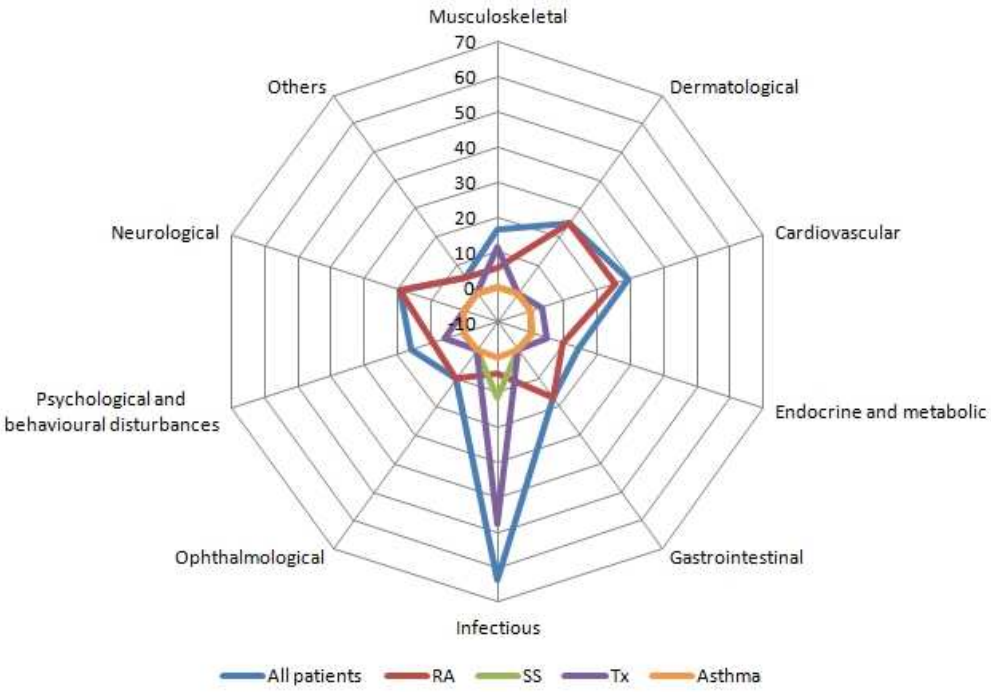


Figure 3 Event rates (events/exposed patients) of adverse events recorded in rheumatoid arthritis (RA), systemic sclerosis (SS), transplantation (Tx) and asthma patients who received intravenous ≥250 mg prednisone equivalent (%).

Table 1 Study characteristics of placebo-controlled studies of pulse glucocorticoids

	Hansen 1990	**Williams 1982**	**Williams 1988**	**Sharada 1994**
Patients (N)	97	20	286	35
Age (years)	60.0	56.0	52.3	33.7
Gender (% female)	73	90	71	91
Disease	RA	RA	RA	SS
Kind of glucocorticoid	MP	MP	MP	D
Cumulative dose#	7875	1250	2308	4000
Study duration (days)	365	84	1689	180
Blind scoring of AE	Yes	Yes	No	Yes
Quality¥	1	2	3	2
Predefined AE	No	Yes	Yes	Yes
AE scoring per protocol	Yes	Yes	Yes	Yes
Missing data*	No	No	Yes	No

Prednisone equivalent (mg)
* Missing data: if the study noted that patients dropped out of the study
¥ Quality of reporting adverse events: studies could score 1 point per criteria with a maximum of 3 points. The three criteria consists of predefined AE, AE scoring per protocol, and missing data.
Abbreviations: RA=rheumatoid arthritis, SS=systemic sclerosis, MP=methylprednisolone, D=dexamethasone

Table 2 Odds ratios of adverse events documented in placebo-controlled studies

Adverse event	Study	Study methodology	Number of patients	Odds ratio (95% CI)	P-value
Musculoskeletal					
Musculoskeletal	Williams 1988	2a	143 vs 143	0.59 (0.14-2.52)	0.48
Osteonecrosis	Williams 1988	2a	143 vs 143	4.09 (0.45-37.02)	0.21
Dermatological					
Dermatological	Williams 1988	2a	143 vs 143	1.21 (0.36-4.05)	0.76
Flushing	Hansen 1990	1b	50 vs 47	14.69 (5.34-40.46)	0.00
Cardiovascular					
Cardiovascular	Williams 1988	2a	143 vs 143	0.50 (0.24-1.06)	0.07
Heart rhythm disorder	Hansen 1990	1b	50 vs 47	2.93 (1.03-8.36)	0.04
Gastrointestinal					
Gastrointestinal	Williams 1988	2a	143 vs 143	0.92 (0.40-2.08)	0.83
Disturbance of taste	Hansen 1990	1b	50 vs 47	5.06 (1.55-16.54)	0.01
Endocrine and metabolic					
Endocrine and metabolic	Williams 1988	2a	143 vs 143	0.16 (0.02-1.35)	0.09
Infectious					
Lower respiratory tract infection	Sharada 1994	1b	17 vs 18	5.62 (1.18-26.85)	0.03
Skin infection	Sharada 1994	1b	17 vs 18	1.07 (0.13-8.56)	0.95
Dental infection	Sharada 1994	1b	17 vs 18	1.06 (0.06-18.45)	0.97
Neurological					
Neurological	Williams 1988	2a	143 vs 143	2.03 (0.37-11.26)	0.42
Headache	Hansen 1990	1b	50 vs 47	6.19 (2.33-16.43)	0.00
Ophthalmological					
Glaucoma	Williams 1982	1b	10 vs 10	3.32 (0.12-91.60)	0.48
Others					
Haematological	Williams 1988	2a	143 vs 143	5.07 (0.24-106.56)	0.30
Genitourinary	Williams 1988	2a	143 vs 143	0.38 (0.12-1.25)	0.11
Others	Williams 1988	2a	143 vs 143	3.02 (0.12-74.78)	0.50

Study methodology as described in Box 1.

Table 3 Top 20 of adverse events reported in nonplacebo-controlled studies

	Adverse event	Event rate (%)	Events/exposed patients	Study groups reporting AE (N)
1	Increased diastolic blood pressure	88	44/50	1
2	Bacterial infections	65.8	25/38	2
3	Viral infections	34.2	13/38	2
4	Hypertension	31.6	12/38	2
5	Diabetes mellitus	24.1	27/112	4
6	Flushing	24.0	12/50	1
7	Osteonecrosis	21.1	30/142	3
8	Headache	20.0	10/50	1
9	Angina pectoris	20.0	1/5	1
10	Hepatitis	18.4	7/38	2
11	Osteoporosis	18.2	16/88	3
12	Heart rhythm disorders	18.2	10/55	2
13	Disturbance of taste	18.0	9/50	1
14	Moon face	18.0	9/50	1
15	Gastroduodenal ulcer	14.0	7/50	1
16	Fungal infections	13.2	5/38	2
17	Psychiatric disorders	13.2	5/38	2
18	Cataract	10.0	5/50	1
19	Dizziness	10.0	5/50	1
20	Pollacisuria	9.1	2/22	1

Discussion

To our knowledge, this is the first study that presents an overview of adverse events of intravenous pulse glucocorticoids (≥250 mg prednisone equivalent) in patients with inflammatory diseases and in patients who underwent transplantation. It is striking that after approximately 50 years of intravenous pulse glucocorticoid use in clinical practice, the prevalence of adverse events is still unknown. Therefore, this study was set up to report intravenous glucocorticoid-related adverse events present in the literature.

Of the 10 included studies, the overall adverse event rate was 44/100 person-years. Cardiovascular and infectious adverse events were mostly documented. In patients who had transplantation, infectious and musculoskeletal adverse events were more frequently documented than cardiovascular, endocrine and metabolic, and psychological and behavioural adverse events. In systemic sclerosis patients only infections were reported. Only in one asthma patient an adverse event was noted, namely diabetes mellitus. In RA patients the most adverse events were documented, with cardiovascular and dermatological adverse events leading. There were 4 placebo-controlled studies in which patients recording flushing had the highest odds ratio, followed by headache, lower respiratory tract infection, disturbance of taste, and heart rhythm disorders. Most of the reported adverse events gave a high risk, though this was not significant.

Many of the adverse events classified by Da Silva *et al.* were also reported in the included studies. Mainly osteoporosis, osteonecrosis, flushing, heart rhythm disorders, disturbance of taste, headache, and glaucoma occurred in the placebo-controlled studies. Probably, with intravenous pulse glucocorticoids there is a higher risk to get these adverse events. We expected that hypertension, diabetes mellitus, euphoria, and psychosis would also belong to this list. In the nonplacebo-controlled studies, patients recording increased diastolic blood pressure had the highest event rate, followed by bacterial and viral infections. Though, diabetes mellitus, osteonecrosis, and osteoporosis were more often mentioned in various study groups.

It was remarkable that only 10 studies met our criteria. Frequently studies were excluded because they focused on functionality of glucocorticoids and assessed treatment effects and not adverse events that were caused by glucocorticoids. In almost all studies concomitant drugs were used, such as disease-modifying antirheumatic drugs (DMARDs) and non-steroidal anti-inflammatory drugs (NSAIDs). Due to this, these drugs could interfere with the reported adverse events. Contemporary, patients receive concomitant drugs to provide a better therapy. Due to this we found only studies of the 1980s that reported adverse events of glucocorticoids without concomitant drugs.

To take the present therapy into account, we included the following criteria that one concomitant drug was allowed. Though, this drug may not be initiated together with the glucocorticoid.

Often, adverse events were not registered numeral but reported on the mean level of the study group, this was done for instance with glucose levels, weight, and blood pressure. These studies could not be included because mean levels give no insight in the prevalence of adverse events, because the number of patients who had an adverse event was not known. Therefore, we agree with the recommendation of van der Goes *et al.* to report the number of patients who had an adverse event(17).

The studies that were included had a wide range of study duration, from 2 days to 4,5 years. The study of Marquette *et al.* had no follow up, and due to this they only reported short term adverse events. This could give an underestimation of the documented adverse events because often adverse events are noticed after a long period. Weusten *et al.* reported both short term as long term adverse events. Not only the study duration had a wide range but also the study population, ranging from 5 patients per group to 143 patients per group. Frequently, the number of patients per group was approximately 20 patients. Due to these small sizes of studies there is a possibility of a type II (β) error.

Another critical point is that some studies reported adverse events while these are related to the patients' history or the underlying disease. For instance, Marquette *et al.* reported diabetes mellitus as adverse event while this patient was already known to have impaired glucose intolerance(12). Though, reported adverse events could also be linked with the underlying disease. For instance, osteoporosis is linked to glucocorticoids but also to active disease in RA.

In conclusion, only relatively few studies are present in the literature that report intravenous pulse glucocorticoid-related adverse events. Generally, these studies are not placebo-controlled, but compare glucocorticoids with other glucocorticoids or drugs. Because of this, an accurate risk assessment can not be done. The primary goals of most studies were to report the beneficial effects of intravenous glucocorticoids and not their adverse events. These data are usually known, which leads to an underestimation of the prevalence of intravenous glucocorticoid-related complications. To overcome this, all results should be reported and not only the beneficial treatment effects. Furthermore, to get an insight into the prevalence of adverse events, the adverse events should be documented in number of patients who developed a specific adverse event.

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Further, I would like to thank dr. Hans Jacobs for his help during this project. You were a great help in analysing the data and in making common sense tables and figures.

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Appendix 1 General systematic literature search

Database:	Searchstring:	Number of studies:
Pubmed	("asthma"[MeSH Major Topic] NOT ("asthma, aspirin-induced"[MeSH Terms] OR aspirin induced asthma[Title/Abstract] OR NSAID-induced asthma[Title/Abstract] OR aspirin-induced asthma syndrome[Title/Abstract]) OR "rheumatic diseases"[MeSH Major Topic] OR "rheumatic disease"[Title/Abstract] OR "rheumatic diseases"[Title/Abstract] OR "rheumatoid arthritis"[Title/Abstract] OR "arthritis, rheumatoid"[MeSH Major Topic] OR "polymyalgia rheumatica"[MeSH Terms] OR "lupus erythematosus, systemic"[MeSH Terms] OR "polymyositis"[MeSH Terms] OR "dermatomyositis"[MeSH Terms] OR "giant cell arteritis"[MeSH Terms] OR "takayasu arteritis"[MeSH Terms] OR "polyarteritis nodosa"[MeSH Terms] OR "wegener granulomatosis"[MeSH Terms] OR "microscopic polyangiitis"[MeSH Terms] OR "churg-strauss syndrome"[MeSH Terms] OR "behcet syndrome"[MeSH Terms] OR "sarcoidosis"[MeSH Major Topic] OR "polychondritis, relapsing"[MeSH Terms] OR "shock, septic"[MeSH Terms] OR "inflammatory bowel diseases"[MeSH Major Topic] OR "inflammatory bowel disease"[Title/Abstract] OR "inflammatory bowel diseases"[Title/Abstract] OR "pulmonary disease, chronic obstructive"[MeSH Major Topic] OR "chronic obstructive pulmonary disease"[Title/Abstract] OR COPD[Title/Abstract] OR "scleroderma, systemic"[MeSH Terms] OR ("transplantation"[MeSH Terms] OR "organ transplantation"[MeSH Terms])) **AND** (("Glucocorticoids/therapeutic use"[Mesh] OR glucocorticoids[MeSH Terms] OR prednisolone[MeSH Terms] OR prednisone[MeSH Terms] OR predniso*[Title/Abstract] OR dexamethasone[MeSH Terms] OR methylprednisolone[MeSH	559

	Terms] OR budesonide[MeSH Terms] OR triamcinolone[MeSH Terms] OR deflazacort[Title/Abstract] OR hydrocortisone[MeSH Terms] OR cortisone[MeSH Terms] OR solumedrol[Title/Abstract] OR "solu medrol"[Title/Abstract] OR depomedrol[Title/Abstract] OR "depo medrol"[Title/Abstract]) AND ("7.5 mg"[Title/Abstract] OR "7,5 mg"[Title/Abstract] OR "10 mg"[Title/Abstract] OR "15 mg"[Title/Abstract] OR "20 mg"[Title/Abstract] OR "25 mg"[Title/Abstract] OR "30 mg"[Title/Abstract] OR "40 mg"[Title/Abstract] OR "60 mg"[Title/Abstract] OR "80 mg"[Title/Abstract] OR "100 mg"[Title/Abstract] OR "120 mg"[Title/Abstract] OR "200 mg"[Title/Abstract] OR "1000 mg"[Title/Abstract] OR "high dose"[Title/Abstract] OR "high dose glucocorticoid"[Title/Abstract] OR "high dose glucocorticoids"[Title/Abstract] OR "medium dose"[Title/Abstract] OR "high dosages"[Title/Abstract] OR "moderate dose"[Title/Abstract] OR "medium dosages"[Title/Abstract] OR "moderate dosages"[Title/Abstract]) AND (Oral[Title/Abstract] OR intramuscular[Title/Abstract] OR intravenous[Title/Abstract] OR "pulse treatment"[Title/Abstract] OR "pulse therapy"[Title/Abstract] NOT (topical[Title/Abstract] OR transdermal[Title/Abstract] OR nasal[Title/Abstract] OR intranasal[Title/Abstract] OR rectal[Title/Abstract]))) **AND** ("adverse effect"[Title/Abstract] OR "adverse effects"[Title/Abstract] OR "adverse event"[Title/Abstract] OR "adverse events"[Title/Abstract] OR "side effect"[Title/Abstract] OR "side effects"[Title/Abstract] OR "side-effect"[Title/Abstract] OR "side-effects"[Title/Abstract] OR "unwanted effect"[Title/Abstract] OR "unwanted effects"[Title/Abstract] OR "osteoporosis"[MeSH Terms] OR "osteonecrosis"[MeSH Terms] OR "muscle weakness"[MeSH Terms] OR "glucose intolerance"[MeSH Terms] OR "diabetes mellitus"[MeSH Terms] OR "weight	

	gain"[MeSH Terms] OR "hyperglycemia"[MeSH Terms] OR "menstruation disturbances"[MeSH Terms] OR "dyslipidemias"[MeSH Terms] OR "atherosclerosis"[MeSH Terms] OR "hypertension"[MeSH Terms] OR "edema"[MeSH Terms] OR "heart failure"[MeSH Terms] OR "water-electrolyte imbalance"[MeSH Terms] OR "myocardial infarction"[MeSH Terms] OR "coronary artery disease"[MeSH Terms] OR "tachycardia, sinus"[MeSH Terms] OR "hypokalemia"[MeSH Terms] OR "hypocalcemia"[MeSH Terms] OR "hirsutism"[MeSH Terms] OR "alopecia"[MeSH Terms] OR "hypertrichosis"[MeSH Terms] OR "cushing syndrome"[MeSH Terms] OR "purpura"[MeSH Terms] OR "cataract"[MeSH Terms] OR "glaucoma"[MeSH Terms] OR "peptic ulcer"[MeSH Terms] OR "pancreatitis"[MeSH Terms] OR "candidiasis"[MeSH Terms] OR "depression"[MeSH Terms] OR "anxiety"[MeSH Terms] OR "irritable mood"[MeSH Terms] OR "dizziness"[MeSH Terms] OR "tinnitus"[MeSH Terms] OR "carcinoma"[MeSH Terms] OR "thrombocytopenia"[MeSH Terms] OR "leukopenia"[MeSH Terms] OR "leukocytosis"[MeSH Terms] OR "proteinuria"[MeSH Terms] OR "arrhythmias, cardiac"[MeSH Terms] OR "hypernatremia"[MeSH Terms] OR "bone loss"[Title/Abstract] OR "Vertebral deformity"[Title/Abstract] OR "Vertebral deformities"[Title/Abstract] OR "fracture"[Title/Abstract] OR "fractures"[Title/Abstract] OR "bone mineral density"[Title/Abstract] OR "bone density"[Title/Abstract] OR myopathy[Title/Abstract] OR "blood glucose"[Title/Abstract] OR "fasting glucose"[Title/Abstract] OR "urine glucose"[Title/Abstract] OR "glycosuria"[Title/Abstract] OR "adipositas"[Title/Abstract] OR "buffalo hump"[Title/Abstract] OR "hyperlipidemia"[Title/Abstract] OR hyperlipidaemia[Title/Abstract] OR hypercholesterolaemia[Title/Abstract] OR "angina pectoris"[Title/Abstract] OR "blood pressure"[Title/Abstract] OR oedema[Title/Abstract] OR "cardiac insufficiency"[Title/Abstract] OR "fluid retention"[Title/Abstract] OR "facial	

	fullness"[Title/Abstract] OR "facial swelling"[Title/Abstract] OR "moon face"[Title/Abstract] OR "cutaneous atrophy"[Title/Abstract] OR "skin atrophy"[Title/Abstract] OR "skin hemorrhage"[Title/Abstract] OR "skin bleeding"[Title/Abstract] OR striae[Title/Abstract] OR "easy bruisability"[Title/Abstract] OR "easy bruising"[Title/Abstract] OR "wound healing"[Title/Abstract] OR "hair loss"[Title/Abstract] OR "gastric ulcer"[Title/Abstract] OR "gastroduodenal ulcer"[Title/Abstract] OR dyspepsia[Title/Abstract] OR dysfagia[Title/Abstract] OR "gastric hemorrhage"[Title/Abstract] OR "stomach hemorrhage"[Title/Abstract] OR "gastroduodenal hemorrhage"[Title/Abstract] OR "viral infection"[Title/Abstract] OR "fungal infection"[Title/Abstract] OR "bacterial infection"[Title/Abstract] OR "skin infection"[Title/Abstract] OR "urinary infection"[Title/Abstract] OR "respiratory infection"[Title/Abstract] OR infection[Title/Abstract] OR libido[Title/Abstract] OR infertility[Title/Abstract] OR palpitation[Title/Abstract] OR psychosis[Title/Abstract] OR euphoria[Title/Abstract] OR seizures[Title/Abstract] OR tremor[Title/Abstract] OR "mood disturbance"[Title/Abstract] OR "mood lability"[Title/Abstract])	
Embase	(('asthma'/exp NOT ('asthma, aspirin-induced'/exp OR 'aspirin induced asthma'/exp OR 'nsaid-induced asthma'/exp OR 'aspirin-induced asthma'/exp) OR 'rheumatic disease'/exp OR 'rheumatic diseases'/exp OR 'rheumatoid arthritis'/exp OR 'arthritis, rheumatoid'/exp OR 'polymyalgia rheumatica'/exp OR 'lupus erythematosus, systemic'/exp OR 'polymyositis'/exp OR 'dermatomyositis'/exp OR 'giant cell arteritis'/exp OR 'takayasu arteritis'/exp OR 'polyarteritis nodosa'/exp OR 'wegener granulomatosis'/exp OR 'microscopic polyangiitis'/exp OR 'churg-strauss syndrome'/exp OR 'behcet syndrome'/exp OR 'sarcoidosis'/exp OR 'polychondritis, relapsing'/exp OR 'shock, septic'/exp OR 'inflammatory bowel disease'/exp OR 'inflammatory	573

	bowel diseases'/exp OR 'pulmonary disease, chronic obstructive'/exp OR 'chronic obstructive pulmonary disease'/exp OR 'copd'/exp OR 'scleroderma, systemic'/exp OR 'transplantation'/exp) AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [review]/lim OR [short survey]/lim) AND ([adult]/lim OR [aged]/lim) AND [humans]/lim) ***AND*** (('glucocorticoids'/exp OR 'glucocorticoid'/exp OR 'prednisolone'/exp OR 'prednisone'/exp OR predniso* OR 'dexamethasone'/exp OR 'methylprednisolone'/exp OR 'budesonide'/exp OR 'triamcinolone'/exp OR 'deflazacort'/exp OR 'hydrocortisone'/exp OR 'cortisone'/exp OR 'solumedrol'/exp OR 'solu medrol'/exp OR 'depomedrol'/exp OR 'depo medrol'/exp) AND ('7.5 mg' OR '10 mg' OR '15 mg' OR '20 mg' OR '25 mg' OR '30 mg' OR '40 mg' OR '60 mg' OR '80 mg' OR '100 mg' OR '120 mg' OR '200 mg' OR '1000 mg' OR 'high dose'/exp OR 'drug megadose'/exp) AND (('oral'/exp OR 'intravenous'/exp OR 'drug pulse therapy'/exp OR 'short course therapy'/exp OR 'intramuscular'/exp) NOT ('rectal'/exp OR 'transdermal'/exp OR 'topical'/exp OR 'intranasal drug administration'/exp)) AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [review]/lim OR [short survey]/lim) AND ([adult]/lim OR [aged]/lim) AND [humans]/lim) ***AND***	

	(('adverse effect'/exp OR 'side effect'/exp OR 'side-effect'/exp OR 'osteoporosis'/exp OR 'osteonecrosis'/exp OR 'muscle weakness'/exp OR 'glucose intolerance'/exp OR 'diabetes mellitus'/exp OR 'weight gain'/exp OR 'hyperglycemia'/exp OR 'menstruation disturbances'/exp OR 'dyslipidemias'/exp OR 'atherosclerosis'/exp OR 'hypertension'/exp OR 'edema'/exp OR 'heart failure'/exp OR 'water-electrolyte imbalance'/exp OR 'myocardial infarction'/exp OR 'coronary artery disease'/exp OR 'tachycardia, sinus'/exp OR 'hypokalemia'/exp OR 'hypocalcemia'/exp OR 'hirsutism'/exp OR 'alopecia'/exp OR 'hypertrichosis'/exp OR 'cushing syndrome'/exp OR 'purpura'/exp OR 'cataract'/exp OR 'glaucoma'/exp OR 'peptic ulcer'/exp OR 'pancreatitis'/exp OR 'candidiasis'/exp OR 'depression'/exp OR 'anxiety'/exp OR 'irritable mood'/exp OR 'dizziness'/exp OR 'tinnitus'/exp OR 'carcinoma'/exp OR 'thrombocytopenia'/exp OR 'leukopenia'/exp OR 'leukocytosis'/exp OR 'proteinuria'/exp OR 'arrhythmias, cardiac'/exp OR 'hypernatremia'/exp OR 'bone loss'/exp OR 'vertebral deformity'/exp OR 'fracture'/exp OR 'fractures'/exp OR 'bone mineral density'/exp OR 'bone density'/exp OR 'myopathy'/exp OR 'blood glucose'/exp OR 'urine glucose'/exp OR 'glycosuria'/exp OR 'adipositas'/exp OR 'hyperlipidemia'/exp OR 'hyperlipidaemia'/exp OR 'hypercholesterolaemia'/exp OR 'angina pectoris'/exp OR 'blood pressure'/exp OR 'oedema'/exp OR 'cardiac insufficiency'/exp OR 'fluid retention'/exp OR 'face edema'/exp OR 'moon face'/exp OR 'cutaneous atrophy'/exp OR 'skin atrophy'/exp OR 'skin hemorrhage'/exp OR 'skin bleeding'/exp OR 'striae'/exp OR 'easy bruisability'/exp OR 'restlessness'/exp OR 'wound healing'/exp OR 'hair loss'/exp OR 'gastric ulcer'/exp OR 'gastroduodenal ulcer'/exp OR 'dyspepsia'/exp OR 'dysphagia'/exp OR 'gastric hemorrhage'/exp OR 'stomach hemorrhage'/exp OR 'gastroduodenal hemorrhage'/exp OR 'viral infection'/exp OR 'fungal infection'/exp OR 'bacterial infection'/exp OR 'skin infection'/exp OR 'urinary infection'/exp OR 'respiratory	

	infection'/exp OR 'infection'/exp OR 'libido'/exp OR 'infertility'/exp OR 'palpitation'/exp OR 'psychosis'/exp OR 'euphoria'/exp OR 'seizures'/exp OR 'tremor'/exp OR 'mood disturbance'/exp OR 'mood lability'/exp) AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [review]/lim OR [short survey]/lim) AND ([adult]/lim OR [aged]/lim) AND [humans]/lim	
Cochrane	(asthma NOT ("asthma, aspirin-induced" OR "aspirin induced asthma" OR "NSAID-induced asthma" OR "aspirin-induced asthma syndrome")) OR "rheumatic diseases" OR "rheumatic disease" OR "rheumatic diseases" OR "rheumatoid arthritis" OR "arthritis, rheumatoid" OR "polymyalgia rheumatica" OR "lupus erythematosus, systemic" OR polymyositis OR dermatomyositis OR "giant cell arteritis" OR "takayasu arteritis" OR "polyarteritis nodosa" OR "wegener granulomatosis" OR "microscopic polyangiitis" OR "churg-strauss syndrome" OR "behcet syndrome" OR sarcoidosis OR "polychondritis, relapsing" OR "shock, septic" OR "inflammatory bowel diseases" OR "inflammatory bowel disease" OR "inflammatory bowel diseases" OR "pulmonary disease, chronic obstructive" OR "chronic obstructive pulmonary disease" OR COPD OR "scleroderma, systemic" OR transplantation:ti,ab,kw **AND** glucocorticoids OR prednisolone OR prednisone OR predniso* OR dexamethasone OR methylprednisolone OR budesonide OR triamcinolone OR deflazacort OR hydrocortisone OR cortisone OR solumedrol OR "solu medrol" OR depomedrol OR "depo medrol":ti,ab,kw AND ("7,5 mg" OR "7.5 mg" OR "10 mg" OR "15 mg" OR "20 mg"	279

	OR "25 mg" OR "30 mg" OR "40 mg" OR "60 mg" OR "80 mg" OR "100 mg" OR "120 mg" OR "200 mg" OR "1000 mg" OR "high dose" OR "high dose glucocorticoid" OR "high dose glucocorticoids" OR "medium dose" OR "high dosages" OR "moderate dose" OR "medium dosages" OR "moderate dosages"):ti,ab,kw AND (Oral OR intravenous OR "pulse treatment" OR "pulse therapy" OR intramuscular):ti,ab,kw NOT (topical OR transdermal OR nasal OR intranasal OR rectal)):ti,ab,kw **AND** ("adverse effect" OR "adverse effects" OR "adverse event" OR "adverse events" OR "side effect" OR "side effects" OR "side-effect" OR "side-effects" OR "unwanted effect" OR "unwanted effects" OR osteoporosis OR osteonecrosis OR "muscle weakness" OR "glucose intolerance" OR "diabetes mellitus" OR "weight gain" OR hyperglycemia OR "menstruation disturbances" OR dyslipidemias OR atherosclerosis OR hypertension OR edema OR "heart failure" OR "water-electrolyte imbalance" OR "myocardial infarction" OR "coronary artery disease" OR "tachycardia, sinus" OR hypokalemia OR hypocalcemia OR hirsutism OR alopecia OR hypertrichosis OR "cushing syndrome" OR "purpura" OR "cataract" OR "glaucoma" OR "peptic ulcer" OR pancreatitis OR candidiasis OR depression OR anxiety OR "irritable mood" OR dizziness OR tinnitus OR carcinoma OR thrombocytopenia OR leukopenia OR leukocytosis OR proteinuria OR "arrhythmias, cardiac" OR hypernatremia OR hypernatraemia OR "bone loss" OR "Vertebral deformity" OR "Vertebral deformities" OR "fracture" OR "fractures" OR "bone mineral density" OR "bone density" OR myopathy OR "blood glucose" OR "fasting glucose" OR "urine glucose" OR glycosuria OR adipositas OR "buffalo hump" OR hyperlipidemia OR hyperlipidaemia OR hypercholesterolaemia OR "angina pectoris" OR "blood pressure" OR oedema OR "cardiac insufficiency" OR "fluid retention" OR "facial fullness" OR "facial swelling" OR "moon face" OR "cutaneous atrophy" OR "skin	

	atrophy" OR "skin hemorrhage" OR "skin bleeding" OR striae OR "easy bruisability" OR "easy bruising" OR "wound healing" OR "hair loss" OR "gastric ulcer" OR "gastroduodenal ulcer" OR dyspepsia OR dysphagia OR "gastric hemorrhage" OR "stomach hemorrhage" OR "gastroduodenal hemorrhage" OR "viral infection" OR "fungal infection" OR "bacterial infection" OR "skin infection" OR "urinary infection" OR "respiratory infection" OR infection OR libido OR infertility OR palpitation OR psychosis OR euphoria OR seizures OR tremor OR "mood disturbance" OR "mood lability"):ti,ab,kw	
Total number of studies minus duplicates:		1411 –238 = 1173

Appendix 2 Overview of intravenous administered glucocorticoid-related adverse events in non placebo-controlled studies

Musculoskeletal

Adverse event	Author	Study	GC initiation	Disease	Study methodology	Quality	Study duration (days)	Cumulative dose#	Events (N)	Patients receiving GCs (N)	Events/exposed patients (95% CI)	P-value
Osteoporosis	Volpin 2002 (A)	1 g MP with tapering (A) vs 3 days 1 g MP per day (B) (Concomitant cyclosporine A or tacrolimus)	Induction	Tx	1b	2	480	5300	7	18	0.39 (0.20-0.62)	0.35
	Volpin 2002 (B)	1 g MP with tapering (A) vs 3 days 1 g MP per day (B) (Concomitant drugs: cyclosporine A or tacrolimus)	Induction	Tx	1b	2	480	7025	7	20	0.35 (0.18-0.57)	0.19
	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	2	50	0.04 (0.01-0.15)	0.00
Osteonecrosis	Weusten 1996	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	7	50	0.14 (0.07-0.27)	0.00
	Shipley 1988 (B)	40 mg vs 500 mg (A) vs 1 g (B) MP (concomitant drugs: not during the preceding 6 months)	Exacerbation	RA	1b	1	84	1250	1	23	0.04 (0.01-0.25)	0.00
	Saisu 1996	Between 1974-1994 69 patients received MP iv and induction/ maintenance prednisolone (Concomitant drugs: not mentioned)	Induction	Tx	2b	2	90	3786	22	69	0.32 (0.22-0.44)	0.00

in mg prednisone equivalent

Abbreviations: MP=methylprednisolone, D=dexamethasone, GC=glucocorticoids, Tx = transplantation, RA = rheumatoid arthritis

Dermatological

Adverse event	Author	Study	GC initiation	Disease	Study methodology	Quality	Study duration (days)	Cumulative dose#	Events (N)	Patients receiving GCs (N)	Events/exposed patients (95% CI)	P-value
Flushing	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	12	50	0.24 (0.14-0.38)	0.00
Acne	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	0	50	0.01 (0.00-0.14)	0.00
Cuteanous atrophy	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	1	50	0.02 (0.00-0.13)	0.00
Urticaria	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	2	50	0.04 (0.01-0.15)	0.00
Skin changes*	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	3	50	0.06 (0.02-0.17)	0.00

*including purpura

in mg prednisone equivalent

Abbreviations: MP=methylprednisolone, D=dexamethasone, GC=glucocorticoids, RA = rheumatoid arthritis

Cardiovascular

Adverse event	Author	Study	GC initiation	Disease	Study methodology	Quality	Study duration (days)	Cumulative dose#	Events (N)	Patients receiving GCs (N)	Events/exposed patients (95% CI)	P-value
Cardiovascular	Marquette 1995	1 mg/kg vs 6 mg/kg MP¥ (Concomitant drugs: β2-agonists)	Induction	Asthma	1b	2	2	1050	0	24	0.02 (0.00-0.25)	0.01
Hypertension	Volpin 2002 (A)	1 g MP with tapering (A) vs 3 days 1 g MP per day (B) (Concomitant cyclosporine A or tacrolimus)	Induction	Tx	1b	2	480	5300	5	18	0.28 (0.12-0.52)	0.07
	Volpin 2002 (B)	1 g MP with tapering (A) vs 3 days 1 g MP per day (B) (Concomitant drugs: cyclosporine A or tacrolimus)	Induction	Tx	1b	2	480	7025	7	20	0.35 (0.18-0.57)	0.19
Hypokalemia	Marquette 1995	1 mg/kg vs 6 mg/kg MP¥ (Concomitant drugs: β2-agonists)	Induction	Asthma	1b	2	2	1050	0	24	0.02 (0.00-0.25)	0.01
	Weusten 1993	3x 1 g MP or D over a 5 day period, some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	2	50	0.04 (0.01-0.15)	0.00
Angina pectoris	Tvede 1986	1 g MP daily for 2 -3 consecutive days (Concomitant drugs: non-steroidal anti-inflammatory drugs)	Induction/ Exacerbation	RA	2b	2	7	3125	1	5	0.20 (0.03-0.69)	0.22
Heart rhythm disorders*	Tvede 1986	1 g MP daily for 2 -3 consecutive days (Concomitant drugs: non-steroidal anti-inflammatory drugs)	Induction/ Exacerbation	RA	2b	2	7	3125	5	5	0.92 (0.38-1.00)	0.11
	Weusten 1993	3x 1 g MP or D over a 5 day period, some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	5	50	0.10 (0.04-0.22)	0.00
Water-electrolyte	Tvede 1986	1 g MP daily for 2 -3 consecutive days	Induction/ Exacerbation	RA	2b	2	7	3125	0	5	0.08 (0.01-0.62)	0.11

imbalance		(Concomitant drugs: non-steroidal anti-inflammatory drugs)										
Heart failure	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	0	50	0.01 (0.00-0.14)	0.00
Oedema	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	0	50	0.01 (0.00-0.14)	0.00
Increased diastolic blood pressure	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	44	50	0.88 (0.76-0.95)	0.00
Sudden death	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	0	50	0.01 (0.00-0.14)	0.00

in mg prednisone equivalent
¥calculations were done with a body weight of 70 kg.
*including bradycardia and palpitation
Abbreviations: MP=methylprednisolone, D=dexamethasone, GC=glucocorticoids, RA = rheumatoid arthritis, Tx=transplantation

Gastrointestinal

Adverse event	Author	Study	GC initiation	Disease	Study methodology	Quality	Study duration (days)	Cumulative dose#	Events (N)	Patients receiving GCs (N)	Events/exposed patients (95% CI)	P-value
Gastrointestinal	Marquette 1995	1 mg/kg vs 6 mg/kg MP¥ (Concomitant drugs: β2-agonists)	Induction	Asthma	1b	2	2	1050	0	24	0.02 (0.00-0.25)	0.01
Intestinal perforation*	Tvede 1986	1 g MP daily for 2 -3 consecutive days (Concomitant drugs: non-steroidal anti-inflammatory drugs)	Induction/ Exacerbation	RA	2b	2	7	3125	1	5	0.20 (0.03-0.69)	0.22
	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	1	50	0.02 (0.00-0.13)	0.00
Gastroduodenal ulcer	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	7	50	0.14 (0.07-0.27)	0.00
Disturbance of taste	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	9	50	0.18 (0.10-0.31)	0.00
Pancreatitis	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	0	50	0.01 (0.00-0.14)	0.00

in mg prednisone equivalent
¥calculations were done with a body weight of 70 kg.
*including sigmoid perforation and peptic ulcer perforation
Abbreviations: MP=methylprednisolone, D=dexamethasone, GC=glucocorticoids, RA = rheumatoid arthritis

Endocrine and metabolic

Adverse event	Author	Study	GC initiation	Disease	Study methodology	Quality	Study duration (days)	Cumulative dose#	Events (N)	Patients receiving GCs (N)	Events/exposed patients (95% CI)	P-value
Diabetes mellitus	Volpin 2002 (A)	1 g MP with tapering (A) vs 3 days 1 g MP per day (B) (Concomitant cyclosporine A or tacrolimus)	Induction	Tx	1b	2	480	5300	4	18	0.22 (0.09-0.47)	0.03
	Volpin 2002 (B)	1 g MP with tapering (A) vs 3 days 1 g MP per day (B) (Concomitant drugs: cyclosporine A or tacrolimus)	Induction	Tx	1b	2	480	7025	8	20	0.40 (0.21-0.62)	0.37
	Marquette 1995	1 mg/kg vs 6 mg/kg MP¥ (Concomitant drugs: β2-agonists)	Induction	Asthma	1b	2	2	1050	1	24	0.04 (0.01-0.24)	0.00
	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	14	50	0.28 (0.17-0.42)	0.00
Moon face	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	9	50	0.18 (0.10-0.31)	0.00

in mg prednisone equivalent

¥calculations were done with a body weight of 70 kg.

Abbreviations: MP=methylprednisolone, D=dexamethasone, GC=glucocorticoids, RA = rheumatoid arthritis, Tx=transplantation

Infectious

Adverse event	Author	Study	GC initiation	Disease	Study methodology	Quality	Study duration (days)	Cumulative dose#	Events (N)	Patients receiving GCs (N)	Events/exposed patients (95% CI)	P-value
Infections	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	1	50	0.02 (0.00-0.13)	0.00
Viral infections	Volpin 2002 (A)	1 g MP with tapering (A) vs 3 days 1 g MP per day (B) (Concomitant cyclosporine A or tacrolimus)	Induction	Tx	1b	2	480	5300	3	18	0.17 (0.06-0.41)	0.01
	Volpin 2002 (B)	1 g MP with tapering (A) vs 3 days 1 g MP per day (B) (Concomitant drugs: cyclosporine A or tacrolimus)	Induction	Tx	1b	2	480	7025	10	20	0.50 (0.29-0.71)	1.00
Fungal infections	Volpin 2002 (A)	1 g MP with tapering (A) vs 3 days 1 g MP per day (B) (Concomitant cyclosporine A or tacrolimus)	Induction	Tx	1b	2	480	5300	1	18	0.06 (0.01-0.31)	0.01
	Volpin 2002 (B)	1 g MP with tapering (A) vs 3 days 1 g MP per day (B) (Concomitant drugs: cyclosporine A or tacrolimus)	Induction	Tx	1b	2	480	7025	4	20	0.20 (0.08-0.43)	0.01
Bacterial infections	Volpin 2002 (A)	1 g MP with tapering (A) vs 3 days 1 g MP per day (B) (Concomitant cyclosporine A or tacrolimus)	Induction	Tx	1b	2	480	5300	9	18	0.5 (0.28-0.72)	1.00
	Volpin 2002 (B)	1 g MP with tapering (A) vs 3 days 1 g MP per day (B) (Concomitant drugs: cyclosporine A or tacrolimus)	Induction	Tx	1b	2	480	7025	16	20	0.80 (0.57-0.92)	0.01
Hepatitis	Volpin 2002 (A)	1 g MP with tapering (A) vs 3 days 1 g MP per day (B) (Concomitant cyclosporine A or	Induction	Tx	1b	2	480	5300	3	18	0.17 (0.06-0.41)	0.01

		tacrolimus)										
	Volpin 2002 (B)	1 g MP with tapering (A) vs 3 days 1 g MP per day (B) (Concomitant drugs: cyclosporine A or tacrolimus)	Induction	Tx	1b	2	480	7025	4	20	0.20 (0.08-0.43)	0.01
Urinary tract infection	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	4	50	0.08 (0.03-0.20)	0.00

in mg prednisone equivalent
Abbreviations: MP=methylprednisolone, D=dexamethasone, GC=glucocorticoids, RA = rheumatoid arthritis, Tx=transplantation

Ophthalmological

Adverse event	Author	Study	GC initiation	Disease	Study methodology	Quality	Study duration (days)	Cumulative dose#	Events (N)	Patients receiving GCs (N)	Events/exposed patients (95% CI)	P-value
Glaucoma	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	0	50	0.01 (0.00-0.14)	0.00
Cataract	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	5	50	0.10 (0.04-0.22)	0.00

in mg prednisone equivalent
Abbreviations: MP=methylprednisolone, D=dexamethasone, GC=glucocorticoids, RA = rheumatoid arthritis

Neurological

Adverse event	Author	Study	GC initiation	Disease	Study methodology	Quality	Study duration (days)	Cumulative dose#	Events (N)	Patients receiving GCs (N)	Events/exposed patients (95% CI)	P-value
Fatigue	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	2	50	0.04 (0.01-0.15)	0.00
Headache	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	10	50	0.20 (0.11-0.33)	0.00
Dizziness	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	5	50	0.10 (0.04-0.22)	0.00
Seizures	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	0	50	0.01 (0.00-0.14)	0.00

in mg prednisone equivalent
Abbreviations: MP=methylprednisolone, D=dexamethasone, GC=glucocorticoids, RA = rheumatoid arthritis

Psychological

Adverse event	Author	Study	GC initiation	Disease	Study methodology	Quality	Study duration (days)	Cumulative dose#	Events (N)	Patients receiving GCs (N)	Events/exposed patients (95% CI)	P-value
Psychiatric disorders	Volpin 2002 (A)	1 g MP with tapering (A) vs 3 days 1 g MP per day (B) (Concomitant cyclosporine A or tacrolimus)	Induction	Tx	1b	2	480	5300	1	18	0.06 (0.01-0.31)	0.01
	Volpin 2002 (B)	1 g MP with tapering (A) vs 3 days 1 g MP per day (B) (Concomitant drugs: cyclosporine A or tacrolimus)	Induction	Tx	1b	2	480	7025	4	20	0.20 (0.08-0.43)	0.01
Delirium	Marquette 1995	1 mg/kg vs 6 mg/kg MP¥ (Concomitant drugs: β2-agonists)	Induction	Asthma	1b	2	2	1050	0	24	0.02 (0.00-0.25)	0.01
Depression	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	0	50	0.01 (0.00-0.14)	0.00
Psychosis	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	0	50	0.01 (0.00-0.14)	0.00
Sleep disturbance	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	2	50	0.04 (0.01-0.15)	0.00
Anxiety	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	2	50	0.04 (0.01-0.15)	0.00
Mood disturbance	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more	Exacerbation	RA	2b	3	1387	8900	4	50	0.08 (0.03-0.20)	0.00

		than 1 pulse regimen (Concomitant drugs: DMARDS)										

in mg prednisone equivalent
¥calculations were done with a body weight of 70 kg.
Abbreviations: MP=methylprednisolone, D=dexamethasone, GC=glucocorticoids, RA = rheumatoid arthritis

Others

Adverse event	Author	Study	GC initiation	Disease	Study methodology	Quality	Study duration (days)	Cumulative dose#	Events (N)	Patients receiving GCs (N)	Events/exposed patients (95% CI)	P-value
Polla.cisuria	Shipley 1988 (A)	40 mg vs 500 mg (A) vs 1 g (B) MP (concomitant drugs: not during the preceding 6 months)	Exacerbation	RA	1b	1	84	625	2	22	0.09 (0.02-0.30)	0.00
Anaphylactic shock	Weusten 1993	3x 1 g MP or D over a 5 day period (some patients received more than 1 pulse regimen (Concomitant drugs: DMARDS)	Exacerbation	RA	2b	3	1387	8900	0	50	0.01 (0.00-0.14)	0.00

in mg prednisone equivalent
Abbreviations: MP=methylprednisolone, D=dexamethasone, GC=glucocorticoids, RA = rheumatoid arthritis

Severe AE*

Author	Study	GC initiation	Disease	Study methodology	Quality	Study duration (days)	Cumulative dose#	Events (N)	Patients receiving GCs (N)	Events/exposed patients (95% CI)	P-value
Shipley 1988 (A)	40 mg vs 500 mg (A) vs 1 g (B) MP (concomitant drugs: not during the preceding 6 months)	Exacerbation	RA	1b	1	84	625	1	22	0.05 (0.01-0.26)	0.00

in mg prednisone equivalent
*1 patient had increased urinary frequency and nocturia
Abbreviations: MP=methylprednisolone, GC=glucocorticoids, RA = rheumatoid arthritis