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

N.A.M. Smits, N. Duru, J.W.J. Bijlsma, J.W.G. Jacobs

Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands.

Noortje A.M. Smits, BSc
Nurten Duru, MD
J.W.J. Bijlsma, MD, PhD, Professor
J.W.G. Jacobs, MD, PhD, Assoc. Prof.

Please address correspondence to:
J.W.G. Jacobs, MD, PhD,
Department of Rheumatology and Clinical Immunology, F02.127,
University Medical Center Utrecht,
Box 85500, 3508 GA Utrecht,
The Netherlands.
E-mail: J.W.G.Jacobs@UMCUtrecht.nl

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ABSTRACT

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

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 GC-related AEs in patients with inflammatory diseases were retrieved.*

Results. *In only 8 studies (344 patients), 4 placebo-controlled and 4 not placebo-controlled studies, intravenous pulse GC-related AEs had been documented (in total 323 AEs), with an AE rate of 35/100 patient-years. In the 4 placebo-controlled studies among RA and systemic sclerosis patients, most of the odds ratios of individual AEs were not statistically significant, except for flushing, heart rhythm disorder, disturbance of taste, lower respiratory infection, and headache. In the 4 not placebo-controlled studies increased diastolic blood pressure was most frequent, followed by flushing and diabetes mellitus. Adverse events seen in more than 15% of patients of all included studies were increased blood pressure, flushing, headache, disturbance of taste, tachycardia and hyperglycemia.*

Conclusion. *GC pulse therapy results in a high AE rate, i.e. 35/100 patient-years. Cardiovascular AEs are most frequently reported in the literature. Furthermore, flushing had the highest odds ratio in the placebo-controlled studies and also a high event rate in the not placebo-controlled studies.*

Introduction

Glucocorticoids (GCs) are used in treatment of various allergic and inflammatory conditions, such as rheumatic diseases, inflammatory bowel diseases, and obstructive lung diseases (1). GCs can be given via different routes including intravenous, oral, intramuscular, intra-articular and transdermal routes, and by inhalation. The dose and duration of therapy range from a high dose for short-term to a low dose for long-term therapy. Characteristic schemes of GC therapy are high dosages of ≥30 mg prednisone equivalent daily, medium dosages of 7.5–30 mg, low dosages of ≤7.5 mg prednisone equivalent daily, and pulse therapy of ≥250 mg prednisone equivalent during one or more days (2).

The occurrence of adverse events (AEs) with daily administration of medium doses of glucocorticoids is frequent (3). Therefore, in the 1960s, short-term intravenous pulse dosing was introduced, hoping that GCs would still have their beneficial effects but fewer AEs compared to daily administration (1). Intravenously used GCs, such as methylprednisolone (MP), have stronger anti-inflammatory and immunosuppressive potencies. For example, lymphopenia is more marked in patients who received 80, 250, 500, or 1000 mg intravenous MP than in patients who received oral prednisone in a range of 15 mg to 100 mg, with a dose-response relationship (4). A decrease of approximately 75% in the number of total peripheral circulating lymphocytes was recorded in patients who received intravenous MP (5). In addition, intravenous MP decreases lymphocyte blastogenesis and lymphocyte activation (5, 6). Furthermore, MP inhibits in a dose-dependent manner the adherence of polymorphonuclear leukocytes (PMN) to endothelial cells and as a consequence the migration of PMN from the bloodstream, which results in granulocytosis in the blood (7).

GCs act via three mechanisms; genomic mechanisms, specific non-genomic mechanisms and unspecific non-ge-

nomic mechanisms (8). Genomic effects are mediated by cytosolic GC receptors that alter the gene expression by activating or repressing specific target genes. Non-genomic effects are mediated by steroid-selective membrane receptors (8, 9). Their effects occur in a few minutes, compared genomic effects which occur after at least 30 minutes. An example of a non-genomic effect is the rapid inhibition of p56lck (Lck) and p59fyn (Fyn) kinases by GCs in human T lymphocytes which leads to immunosuppression (10). Unspecific non-genomic mechanisms occur only at high GC dosages. The mode-of-action could be direct interactions with the cellular energy metabolism, which leads to an immunosuppressive effect within seconds. The therapeutic benefits of high-dose intravenous GC therapy could be partly due to these unspecific non-genomic effects (11).

Previously, the risk of AE of low to medium dose GCs have been systemically reviewed (3), but the risks of AEs of administration of pulse glucocorticoids have not been systematically analysed. The aim of this study was to systematically review the literature on reported AEs of intravenous pulse therapy of GCs and to quantify the risk of AEs, independent of the underlying inflammatory disease.

Methods

Literature search

A literature search was performed by the authors NAMS and ND, reviewing GC-related AEs in inflammatory diseases using the bibliographic databases PubMed, Embase, and the Cochrane library. The search consisted of relevant keywords for disease, *e.g.* rheumatic diseases, obstructive lung diseases, and inflammatory bowel diseases, treatment (intravenous pulse therapy), and AEs which was checked by experts (JWGJ and JWJB). The search terms included keywords, words of title or abstract, synonyms, and plurals. MESH terms were added for the PubMed search. All search terms were combined using Boolean operators (see Box 1).

Study selection

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

Box 1. General systemic literature search

Database	Searchstring	n° 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]) **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 Terms] 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 (“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]) AND (intravenous[Title/Abstract] OR “pulse treatment”[Title/Abstract] OR “pulse therapy”[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	64

	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]) Limits activated: Humans, All adults: 19+ years	
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 bowel diseases'/exp OR 'pulmonary disease, chronic obstructive'/exp OR 'chronic obstructive pulmonary disease'/exp OR 'copd'/exp OR 'scleroderma, systemic'/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 'hydrocortisone'/exp OR 'cortisone'/exp OR 'solumedrol'/exp OR 'solu medrol'/exp OR 'depomedrol'/exp OR 'depo medrol'/exp) AND ('40 mg' OR '60 mg' OR '80 mg' OR '100 mg' OR '120 mg' OR '200 mg' OR '1000 mg') AND ('intravenous'/exp OR 'drug pulse therapy'/exp OR 'short course therapy'/exp) NOT ('oral'/exp OR 'intramuscular'/exp OR '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	69

	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"):ti,ab,kw **AND** (glucocorticoids OR prednisolone OR prednisone OR predniso* OR dexamethasone OR methylprednisolone OR hydrocortisone OR cortisone OR solumedrol OR "solu medrol" OR depomedrol OR "depo medrol"): ti,ab,kw AND ("40 mg" OR "60 mg" OR "80 mg" OR "100 mg" OR "120 mg" OR "200 mg" OR "1000 mg"): ti,ab,kw AND (intravenous OR "pulse treatment" OR "pulse therapy"):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	25
Total number of studies minus duplicates:		158 –27= 131

- Study population: adults with inflammatory diseases treated with GCs.
- Intervention: patients who received ≥250 mg prednisone equivalent intravenous pulse therapy for one or more days.
- Outcome: numbers of AEs on patient's level caused by GC treatment.
- Study designs: (randomised) controlled trials, prospective trials, cohort studies, and observational studies.

If only a subgroup of the total study population received intravenous pulse GCs and their stratified data were reported, this subgroup was included in the analysis. Exclusion criteria were case reports, non-English language, and pulse therapy started together with more than one disease-modifying antirheumatic drug (DMARD) or immunosuppressive drug. Only full text available papers were included.

Data extraction

The characteristics of included studies were recorded, like number of patients, gender, age, diagnosis, dose of GC, study duration, patients dropping out from the study (missing data), and deaths. The following information about the reported AEs was collected:

type and number of AEs, the frequency of monitoring, blinding of investigator, and study methodology. AEs were classified in groups, according to classifications used in literature. (3, 12).

Quality assessment

The selected studies were judged for the quality of their assessing and reporting of AEs, using the following criteria (3):

- Predefined AE: yes/no; whether the study applied predefined AEs.
- Standardised AE scoring protocol: yes/no; whether in the study an AEs protocol, *e.g.* questionnaire had been used.
- Missing data: yes/no; whether the study reported the number of missing data and why data was missing, *e.g.* drop outs.

A study could score 0 to 3 quality points (1 point per criterion), where 3 points reflects the highest quality.

Data analysis

AEs of GCs *versus* placebo were analysed calculating odds ratios. Studies without placebo group were analysed with events/exposed patients. Analyses were done by using the Comprehensive Meta-Analysis software (Biostat, Engelwood, New Jersey, USA).

Results

Literature search

Using the specified search strategy (online Appendix), 158 studies were obtained, consisting of 64, 69, and 25 hits in PubMed, Embase, and Cochrane, respectively. Doubles (n=27) were filtered by loading the studies into Reference Manager 11, an electronic bibliographic management system. After screening the titles and abstracts, and reading the full texts, 5 articles met the inclusion criteria. Using the reference lists of the full text available studies another 3 related articles were included. In total, 8 articles described AEs of intravenous GCs. The studies included patients with RA, asthma, and systemic sclerosis. Relevant AE data were extracted from these studies. Only 4 studies compared GCs with placebo (13-16). The other studies were not controlled or compared various dosages of GCs. The different GC groups were analysed separately.

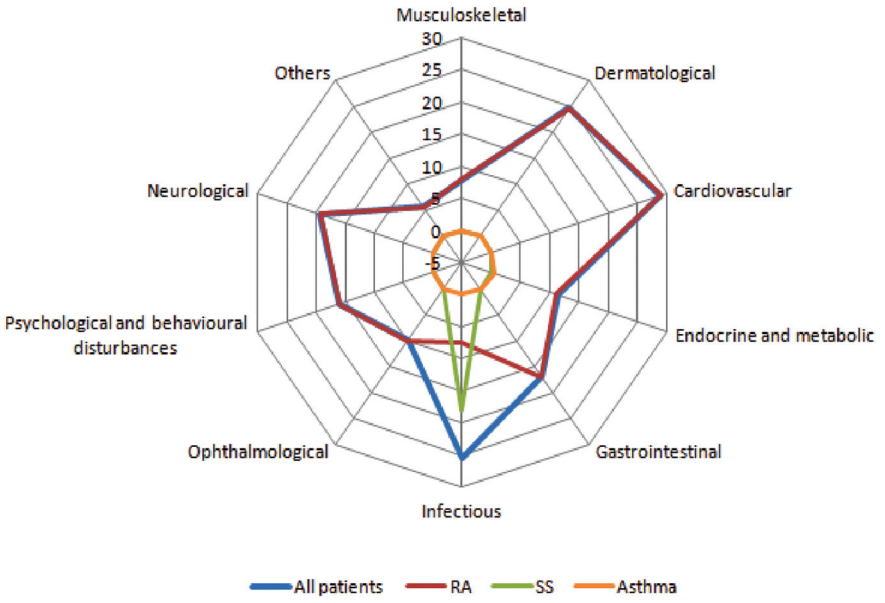

Fig. 1. Number of adverse events of intravenous GC pulse therapy per 100 exposed patients. Total exposed patients n=344 (rheumatoid arthritis (RA): 6 studies, n=303; systemic sclerosis (SS): 1 study, n=17; asthma: 1 study, n=24).

Adverse events of all 8 included studies

In total, 344 patients received intravenous GCs and 323 AEs were recorded, with an AE rate of 35/100 patient-years. Cardiovascular AEs were most often noted, followed by infectious AEs. Dermatological, gastrointestinal, and neurological AEs were only reported in RA patients. In patients with systemic sclerosis, only infections were reported, and one asthma patient developed diabetes mellitus (Fig. 1). Only one AE was classified as severe by the authors, which was nocturia and frequent voiding in an RA patient (17). Adverse events seen in more than 15% of patients of all included studies were increased blood pressure, flushing, headache, disturbance of taste, tachycardia and hyperglycemia.

The 4 placebo-controlled studies

The study characteristics of these 4 studies are listed in Table I. In total, 220 patients received high pulse intravenous GCs and 218 patients received placebo. One study reported on systemic sclerosis patients receiving intravenous dexamethasone (14). In other studies, patients with RA or asthma received MP. The quality of reporting AEs of these studies was 1, 2, 3, and 2, and the length of the study ranged from 3 months to 4.5 years approximately. Three of the studies were randomised double-blinded controlled trials and one was a non-randomised controlled trial.

The overall odds ratio of reported AEs in these placebo-controlled studies was 1.83 with an 95% confidence interval (CI) of 0.98–3.40 (p-value 0.06). Most of the odds ratios of individual AEs were not statistically significant, except for flushing, heart rhythm disorder, disturbance of taste, lower respiratory infection, and headache (Table II), showing an increased risk associated with intravenous GCs, compared to placebo. The odds ratio of flushing was highest: 15 (95% CI 5.3–40), followed by that for headache: 6.2 (95% CI 2.3–16).

The 4 not placebo-controlled studies

Of the 4 not placebo-controlled studies, 3 had been performed among patients with RA and 1 among patients with asthma (17-20). In total 124 patients received intravenous pulse GCs and in total 39 different AEs were documented. The top 20 most reported AEs are listed in Table III. The event rate of increased diastolic blood pressure was highest, 88%, followed by event rates of 20% and 24% of flushing and dia-

Table I. Characteristics of the 4 placebo-controlled studies on intravenous pulse GC.

	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 GC	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 consist of predefined AE, AE scoring per protocol, and missing data.
RA: rheumatoid arthritis; SS: systemic sclerosis; MP: methylprednisolone; D: dexamethasone.

betes mellitus, respectively. Diabetes mellitus, heart rhythm disorders, and osteonecrosis were reported in 2 studies; all other AEs had been reported only in one study.

Discussion

To our knowledge, this is the first study that systematically analysed reported AEs of intravenous pulse GCs (≥250 mg prednisone equivalent) in patients with inflammatory diseases. It is striking that after approximately 50 years of intravenous pulse GC use in clinical practice, the prevalence of AEs is not well known. Therefore, this study was undertaken to report intravenous GC-related AEs present in the literature.

It was remarkable that only 8 studies met our criteria. Frequently studies had to be excluded because they focused on treatment effects of GCs and not on AEs. In almost all studies concomitant drugs were used, such as DMARDs and NSAIDs, which could interfere with reported AEs. Nowadays, rheumatologists tend to start earlier concomitant drugs, for example DMARDs in early RA. We found only studies of the 1980s that reported AEs of intravenous GCs without concomitant drugs. We included studies with patients using concomitantly more than one DMARD or immunosuppressive drug, but only if these drugs had not been initiated at the same time as the GC.

Table II. Odds ratios of adverse events recorded in the 4 placebo-controlled studies on intravenous pulse GC.

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

Study methodology: 1: Randomised controlled trial; 2: controlled study without randomisation; others: not specified by authors.

Table III. Top 20 most frequently reported adverse events in the 4 not placebo-controlled studies.*

	Adverse event	Event rate (%)	Events/exposed patients	Number of studies/ subgroups reporting the AE
1	Increased diastolic blood pressure	88	44/50	1
2	Flushing	24	12/50	1
3	Diabetes mellitus	20	15/74	2
4	Angina pectoris	20	1/5	1
5	Headache	20	10/50	1
6	Heart rhythm disorders	18	10/55	2
7	Disturbance of taste	18	9/50	1
8	Moon face	18	9/50	1
9	Gastroduodenal ulcer	14	7/50	1
10	Osteonecrosis	11	8/73	2
11	Cataract	10	5/50	1
12	Dizziness	10	5/50	1
13	Pollacisuria	9	2/22	1
14	Urinary tract infection	8	4/50	1
15	Mood disturbance	8	4/50	1
16	Skin changes	6	3/50	1
17	Osteoporosis	4	2/5	1
18	Urticaria	4	2/50	1
19	Fatigue	4	2/50	1
20	Sleep disturbance	4	2/50	1

*Please note: included studies are characterised by a wide range of study duration and study population, influencing the ranks in this top 20.

Often, AEs were not registered numeral but reported as the mean level of the study group. This was done for instance with glucose levels, weight, and blood pressure. These AEs could not be included because mean levels give no insight into the prevalence of AEs, as the number of patients who suffered from the AE cannot be calculated from means.

Limitation of our meta-analysis is that the included studies were characterised by a wide range of study duration, from 2 days to 4.5 years. One study had no follow up, and due to this they only reported short-term AEs (19). Another study reported both short-term as long-term AEs (20). Also the range of the study population was wide, ranging from only 5 patients per group to 143 patients per group, but the overall number of patients per group was low, approximately 20 patients per group. Another limitation is that some studies reported AEs which could be (partly) also attributed to the patients' history or the underlying disease. For instance, diabetes mellitus was reported as an AE in an asthma patient, while this patient was already known to have impaired glucose intolerance (19). Infections could be linked to the administered GCs but also to the inflammatory disease (21); for instance patients with systemic sclerosis are prone to develop skin ulcer infections and dental infections. Finally, because the primary aim of the studies most frequently had not been analysis of AEs, it was less straightforward to identify studies reporting on AEs from their title and abstract; studies may have been missed.

Most of the reported AEs were mild. For example, the lower respiratory tract infections in the systemic sclerosis patients were minor, not associated with chest x-ray abnormalities or positive sputum cultures. Furthermore, flushing and headache generally are considered to be not severe and temporary. Though, patients often experience these AE as very inconvenient and patients who receive intravenous GCs should be aware of the occurrence of these AEs.

Heart rhythm disorders induced by high-dose GC treatment, like palpitation and tachycardia are more of a clinical problem. They might spontaneously recover, but could be dangerous in patients who have a heart disease. So, acquiring a detailed cardiovascular history is recommended, with attention for high blood pressure and signs of angina pectoris, or a familial cardiovascular risk profile. Independently of these results, before the treatment with intravenous GCs, an ECG should be taken and blood pressure should be monitored in each patient during therapy. Formulating recommendations for monitoring for diabetes mellitus based on this literature search is not possible, other than to check blood glucose levels during the therapy.

In conclusion, intravenous GC pulse therapy results in a high AE rate, namely 35/100 patient-years. Cardiovascular AEs are most frequently reported in the literature, in particular increased diastolic blood pressure and heart rhythm disorders. Furthermore, flushing had the highest odds ratio in the placebo-controlled group and a high event rate in the not placebo-controlled group.

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