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Review

New concepts to reduce glucocorticoid toxicity

Rieke Alten*, Max Mischkewitz

Schlosspark-Klinik Charité University Medicine Berlin, Heubnerweg, 2, 14059 Berlin, Germany

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ABSTRACT

70 years after their first use, low-dose glucocorticoids are a common part of pharmacological rheumatoid arthritis treatment. This is due to their well-proven capacities in symptom severity and disease activity reduction, in particular when combined with a disease-modifying anti-rheumatic drug, such as methotrexate. Nevertheless, glucocorticoid administration, in long-term especially, is also seen critically because of its potential adverse conditions. In order to achieve a reduction in treatment-related adverse events, modern therapy regimes should take into consideration patients' risk factors and therefore be individual. The Glucocorticoid Toxicity Index is a method to measure side effects of glucocorticoid therapy objectively and will be central in future studies comparing different therapy regimes. Such a new therapy regime is modified-release prednisone, which – thanks to a different time of liberation – seems to capable of reducing morning stiffness much more effectively than conventional prednisone, whilst showing similar properties in disease activity reduction and safety. Still, confirmation of these first data in further trials will be necessary. Eventually, other innovative concepts are liposomal glucocorticoids, dissociated agonists of glucocorticoid receptors and intramuscular application of glucocorticoids. Though these approaches appear to be promising, additional research will be required.

1. Introduction

The use of glucocorticoids (GCs) as therapy in Rheumatoid Arthritis (RA) has been first described more than half a century ago. In 1948, Hench et al. treated the first RA patient with Compound E (17-Hydroxy-11-Dehydrocorticosterone). The 29 year-old married woman suffered from severe RA with radiographic evidence of joint destruction and complained about joints being stiff, swollen and tender. Hence, she was almost bedridden. On the second day after the intra-gluteal application of 100 mg of Compound E the patient reported less myalgia and one day later painful morning stiffness had entirely vanished and she was hardly impaired in walking [1]. After having treated more patients with remarkable success, Edward C. Kendal, Tadeus Reichstein and Philip S. Hench were awarded the Nobel Prize in Physiology and Medicine for their research on GCs [2]. In 2016, systemic Corticosteroids were prescribed more than nine million times in Germany alone, summing up to costs of 167.2 million Euros [3].

Thiele et al. observed that about 60% of all German RA patients were treated with oral GCs in 2005, most of them with dosages below or at 7.5 mg daily. Whilst GC monotherapy was barely existing (1.1% of all patients), almost 62% of patients being treated with disease-modifying anti-rheumatic drugs (DMARDs) also received oral GCs. GCs appear to be even more prevalent in patients with DMARD combination therapies (76%) or with tumor necrosis factor- (TNF) inhibitors (72.4%), possibly indicating a more frequent use of GCs in more severe RA [4].

2. Effects of glucocorticoids in rheumatoid arthritis

The merit of GC therapy in RA has been proved by a number of studies. Gøtsche et al. compared the effects of low-dose (not more than a prednisolone equivalent (PEQ) of 15 mg daily) short time oral GCs use to those of placebo or NSAID therapy. Their meta-analysis was able to show the superiority of oral GCs over placebo in joint tenderness, pain and grip strength after about one month of therapy. GC treatment proved to be superior to NSAID therapy as well in joint tenderness and pain, however, superiority in grip strength was not significant [5].

As illustrated before, GCs are rather used in combination with DMARDs than as monotherapy. The CAMERA-II trial was a double-blind, randomized and placebo-controlled study investigating the benefits of a combination therapy of methotrexat (MTX) and low-dose prednisone in patients with early RA. The control group was provided with MTX and placebo. The MTX/prednisone group

* Corresponding autho at: Department of Internal Medicine II, Rheumatology, Clinical Immunology and Osteology, Schlosspark-Klinik, Charité University Medicine Berlin, Heubnerweg, 2, 14059 Berlin, Germany.
E-mail address: rieke.alten@schlosspark-klinik.de (R. Alten).

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showed significantly less erosive joint damage, a significantly lower mean erythrocyte sedimentation rate (ESR) and a significantly higher improvement in the mean Health Assessment Questionnaire (HAQ) after two years. Other parameters of disease activity, such as pain and the Disease Activity Score 28 (DAS28) showed significant improvements after three and six months of therapy [6], indicating a more rapid change than in the MTX/placebo group.

A similar trial by Svensson et al. also found that patients treated with a DMARD and low-dose prednisone show less radiographic progression after two years than those treated with a DMARD and placebo. Moreover, disease activity indices (HAQ and DAS28) decreased more in the group treated with DMARD/prednisone than in the control group. This difference proved to be significant at every examination. Eventually, 55.5% of the patients treated with prednisone entered remission (DAS28 < 2.6), compared to only 32.8% in the control group [7]. These findings substantiate a relevant benefit of a GC therapy for RA patients both in a short and medium period of time.

The long-term efficacy of glucocorticoids has also been investigated. Tengstrand et al. conducted a trial by randomising RA patients who received low-dose prednisolone for at least two years to either continue or withdraw CG therapy. Among 26 patients, 15 determined to withdraw were not able to attain withdrawal in one year and were therefore considered "withdrawal failures". Moreover, average DAS28 over two years was shown to be significantly higher in the withdrawal failure group than in the group treated with prednisolone [8]. A similar study found that patients being withdrawn from low-dose prednisone and shifted towards placebo are more likely to withdraw from the trial due to lack of efficacy than those continuing GC treatment [9]. These withdrawal studies indicate a positive effect of GC therapy on disease activity in RA also in long terms.

Apart from disease activity, also the impact of GC treatment on radiographic progression in RA has been investigated. A Cochrane meta-analysis included 15 either one or two-year studies. In the mean of all studies, there was a significant standardised mean difference (SMD) in favour of GC therapy both after one year and two years of treatment. Accordingly, glucocorticoids are proved to have joint sparing properties in RA [10].

3. Safety

Notwithstanding their above mentioned positive effects in RA patients, GCs remain somehow controversial due to their safety characteristics. It is widely accepted, that the risk of adverse events (AEs) of GC therapy is dependent on both GC dosage and duration as well as patients' individual risk factors. Some of the most disturbing conditions possibly caused by GC administration are alterations in glucose metabolism / Diabetes Mellitus (DM), infections, change in bone mineral density (BMD) and cardiovascular diseases (CVD) [11].

A systematic review by Santiago et al., investigating adverse events in studies comparing low-dose GC treatment to no GC treatment in RA, found a significant increase in mean fasting serum glucose in patients receiving GCs. In other studies, no significant difference could be seen [12]. Interestingly, based on experimental data, RA itself seems to be associated both with impaired β-cell function and altered insulin sensitivity, regardless of whether they receive GC therapy of not. Moreover, impaired glucose metabolism (IGM) and Type 2 Diabetes Mellitus (T2DM) are frequently diagnosed in RA patients [13]. These findings could constitute a bias when trying to determine the influence of GC treatment on glucose metabolism in RA patients.

Meta-analyses conducted by Dixon et al. produced ambiguous results when scrutinizing the incidence of infections in RA patients. Whilst a meta-analysis of Randomised Controlled Trials (RCT) showed no elevated risk of infection in patients receiving GC therapy (risk ratio (RR) = 0.97), an analysis of observational studies clearly indicates an association (RR = 1.67). The latter analysis showed a correlation of GC dosage and risk as well, with daily doses < 5 mg; 5–10 mg and 10–20 mg PEQ leading to RRs of 1.37; 1.93 and 2.97 respectively. This discrepancy between RCTs and observational studies might be attributed to the longer time of GC therapy in the observational studies and therefore the presence of a higher cumulative dose. Nevertheless, these analyses remain somehow uncertain due to a relatively small number of events reported in the RCTs and a significant heterogeneity among the observational studies [14].

Evidence is more unequivocal on post-operative infections in GC treated patients undergoing joint surgery. In a retrospective study by George et al., the incidences of hospitalized infections up to 30 days after surgery and prosthetic joint infections (PJI) of patients receiving GC treatment and several perioperative protocols of TNF-inhibitor infliximab after elective knee and hip arthroplasty were compared. Whilst no differences among the infliximab protocols were seen, GC treatment above 10 mg PEQ daily was associated with an elevated risk of both hospitalized infections up to 30 days after surgery and PJIs [15].

Changes in BMD during low-dose GC therapy in RA patients were examined by a meta-analysis containing seven studies dealing with lumbar and/or femoral BMDs, altogether 353 patients and 343 controls. Results showed a significant loss of lumbar as well as femoral BMDs (standardised mean difference (SMD) = −0.354; SMD = −0.488, respectively). Accordingly, changes in BMD and associated fractures must be taken into consideration, when treating RA patients with low-dose GCs [16].

An extensive systematic review on CVDs and related conditions revealed ambiguous findings. Major cardiovascular risk factors such as high blood pressure and dyslipidaemia could only in some studies be proved to be induced by low-dose GC treatment in RA patients. Similarly, just one of nine articles included showed a significant elevated carotid intima-media thickness correlated to the dose of low-dose GCs, indicating atherosclerosis. Four out of six studies assessing major cardiovascular events (such as myocardial infarction, stroke or heart failure) found an association with GC therapy. Nevertheless, results in some studies only apply to specific events and/or specific doses of GCs. Notwithstanding the inhomogeneous findings, the authors conclude to have identified a "trend" towards an increase of major cardiovascular events in RA patients with low-dose GC therapy [17].

Weight gain seems to be well-attributable to low-dose GC treatment in RA patients, as well as glaucoma and dermatological side effects [12,18]. Purpura, cushingoid phenotype, ecchymosis, skin thinning and easy bruisability can be observed in more than 5% of patient treated with at least 5 mg PEQ daily for not less than one year. The risk of these AEs seems to be rising with elevated GC dosage [18,19]. Though mostly not considered medically severe, skin alterations can prove a relevant burden for the patient [18]. While according to Black et al. data on cataract incidence appears to be quite scarce and heterogeneous [20], cataracts are a well-known possible consequence of long-term GC therapy in the long run [18]. Huscher et al. found a threshold pattern for cataract as a side effect of long-term GC therapy with a threshold below 5 mg per day [19].

Clear conclusion on gastrointestinal and neuropsychological AEs could not be drawn by the systematic review a Santiago et al. [12]. However, on many conditions possibly related to low-dose GC therapy, data is not convincing yet, requiring new studies and analyses.

Moreover, the effects of RA itself can confound the impact of GCs. For example, the chronic pro-inflammatory situation induced by RA might be facilitating insulin resistance. Accordingly, loss in

BMD and negative effects on the cardiovascular system can be consequences of the disease itself as well [11].

4. Individual risk in long-term glucocorticoid therapy

Considering the data mentioned above, it becomes necessary to assess patients' risks in long-term GC therapy individually. For this purpose, Strehl et al. proposed a differentiation based on the dosage and patients' risk factors. They conclude that with a dosage below or at 5 mg/day PEQ patients generally have "an acceptably low level of harm" in causing hyperglycaemia/DM, infections or changes in BMD. Patients already having a high level of risk for CVD might be in need for preventive measures, though. For patients taking more than 10 mg/day PEQ the risk is considerably high, independently from their risk factors. Eventually treatment with more than 5 but not more than 10 mg/day PEQ provides a risk largely depending on individual risk factors [11].

The individual risk factors for adverse events under long-term GC therapy are presented in Table 1, as well as possible preventive measures to reduce the likelihood of harm [11].

5. European league against rheumatism recommendations

Current therapy regimes recommend the use of low-dose GCs in the combination with one or more conventional synthetic DMARD(s) (csDMARD) in the initial period of RA treatment. After a period of six months GCs should be tapered, as fast as possible [21].

In 2007, a multidisciplinary guideline development group of the European league against Rheumatism (EULAR) agreed on their "evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases". Many of these recommendations (Table 2) focus on safety issues possibly related to GCs, i.e. possible AEs, minimisation of dosage in long-term therapy, monitoring of parameters and prevention when necessary and possible. All of the recommendations referred to were agreed upon with a relatively high rate of approval, some even in unison. This emphasises the importance the vast majority of experts attribute to adequate measures to minimise harm by GC treatment [22].

Accordingly, another EULAR research group has formulated recommendations for the monitoring of adverse events in low-dose GC therapy. Though studies of good quality appeared to be scarce, the group developed monitoring schedules both for GC use in clinical trials and daily practice (Table 3) [23].

6. Glucocorticoid toxicity index

To be able to achieve an evident reduction in GC toxicity, it is necessary to develop a measurement for it, as have recently done Miloslavsky et al. Their Glucocorticoid Toxicity Index (GTI) involves 20 domains and 54 items summed up in to lists. The Composite List on one hand contains common adverse conditions, which will be weighed and is able to capture improvement and worsening. The items on the Specific List on the other hand are serious but rare and will not be weighed [24].

The items on the Composite List had to have a probability of occurrence higher than 5% in patients treated with GCs, be independent, be more likely to be the result of the GC exposition rather than disease itself, be unlikely caused by earlier GC treatment and be measured typically without imaging of invasive procedures. If conditions did not meet these criteria, but were considered of importance nonetheless, they were included into the Specific List. The full GTI is depicted in Table 4 [24].

Being an instrument designed to measure toxicity change, measurements at at least two points of time are necessary. The grading of most domains provides the possibility to evaluate change in specific conditions and therefore record worsening or improvement. Furthermore, as soon as a subject develops an item of the Specific List, not only this item, but also the most severe in the same domain on the Composite List will be registered, to enable scoring. In trials, the GTI is recommended to be administered every three months, with the exception of BMD measurements, which are supposed to take place not more than once a year. Moreover, documenting both the total GTI Score and subscores of specific domains is expected to offer a differentiated image of GC toxicity in patients. Eventually also validity and reliability exercises were performed on the GTI presenting excellent results [24]. The development of the GTI was required to significantly evaluate possible AEs caused by GCs. In future trials new GC therapy regimes can be compared to established ones by using this instrument. To consolidate the first promising results of validity and reliability tests, further validation will be necessary.

7. Unclear use of glucocorticoids in rheumatoid arthritis trials

Interestingly, concomitant GC use in RA studies, in particular on biologic treatments, is often reported insufficiently. Whilst at least 85% of the main trials between 1994 and 2010 involving biologic agents state, whether GCs were used or not, the proportion of subjects actually using GCs varies remarkably (34% to 93%) and varies also for specific biologic agents. However, data on dosage and possible dosage variation during the trials are still scarce. Information are also insufficient on flare frequency [25].

Therefore, GCs may constitute a major possible confounding factor in trials investigating biologic drugs in RA, both in terms of efficacy and safety. This is due to the effect of GCs on RA disease activity (particularly if combined with a DMARD) and its possible adverse reactions. Accordingly, reporting on concomitant GC status as well as dosage, dosage variation and duration and other details of interest should be compulsory [25].

8. Modified-release prednisone

The circadian rhythm of secretion of endogenous GCs is already well-known, while more recent research also found circadian rhythms in rheumatic diseases, namely RA, themselves. Thus, the morning peak of endogenous cortisol (about 8:00 am) appears to be only the response to an earlier peak of pro-inflammatory hormones such as interleukin 6 (IL-6), which are at least temporally associated with the occurrence of RA symptoms, such as morning stiffness [26].

To address these specific patterns, modified-release prednisone (MR-prednisone) has been developed. This medication releases its low-dose GC four hours after administration and should be taken about 22:00. Accordingly, prednisone will be liberated at 2:00 am and is supposed to deliver a more efficacious reduction of both symptoms and IL-6 serum concentration. An experimental study by Kirwan et al. investigated duration of morning stiffness, arthritic pain intensity, DAS and serum concentration of pro-inflammatory cytokines and cortisol in patients receiving 5 mg MR-prednisone for 14 days. Subjects were GC naïve and did not change their basic RA treatment [27].

Even though only nine patients were included in the study, significant improvements in morning stiffness, pain, cytokine levels and disease activity could be detected. Morning stiffness decreased by 50% to almost 100% in six subjects, whilst three showed no improvement at all. Interestingly, these three patients also revealed serum concentrations of pro-inflammatory cytokines other than Il-6 [Il-4, Il-1ra, Il-1β, Tumor necrosis factor (TNF)] that were much higher than in the other six subjects (measured before interven-

Table 1
Individual risk factors for adverse events in glucocorticoid therapy (modified according to Strehl et al., 2016).

Risk factors for			
Hyperglycaemia/DM	Infections	Osteoporosis	CVD
Genetic disposition	Dosage	Age	Age
Age	Age (> 60 years)	Female sex	Male sex
Obesity	Male gender	Low body weight	Obesity
Chronic inflammation	Chronic lung, heart, renal diseases	Low BMD	DM
	Certain neurologic diseases	Prevalent fractures	Dyslipidaemia
	Peripheral vascular diseases	Family history of osteoporosis	Active disease, extra-articular manifestations, positive rheumatic factors and/or antibodies to citrullinated proteins (in RA)
	DM		
	Hepatitis C		
	Leucopenia		
	History of prior serious infection		
Possible prevention			
Weight loss in obese patients	Screening for and/or vaccination against, for example, influenza, pneumococci or herpes zoster	Appropriate exercise	Healthy diet (low in saturated fats and calories)
Healthy diet		Sufficient Vitamin D/calcium intake	Appropriate physical activity
Appropriate exercise		Treatment with bisphosphonates, osteoanabloic drugs or selective oestrogen receptor modulators on indication	Sodium restriction
Hydroxochloroquine as therapeutic measure			Cessation of smoking
			Preventive use of statins or ACE-inhibitors on indication

DM: diabetes mellitus; CVD: cardiovascular disease; BMD: bone mineral density; RA: rheumatoid arthritis; ACE: angiotensin-converting enzyme.

Table 2
European League Against Rheumatism recommendations on glucocorticoid therapy in rheumatic diseases (modified according to Hoes et al., 2007).

Proposition		
1	a	The adverse effects of glucocorticoid therapy should be considered and discussed with the patient before glucocorticoid therapy is started
	b	This advice should be reinforced by giving information regarding glucocorticoid management
	c	If glucocorticoids are to be used for a more prolonged period of time, a “glucocorticoid card” is to be issued to every patient, with the date of commencement of treatment, the initial dosage and the subsequent reductions and maintenance regimes
2	a	Initial dose, dose reduction and long-term dosing depend on the underlying rheumatic disease, disease activity, risk factors and individual responsiveness of the patient
	b	Timing may be important, with respect to the circadian rhythm both of the disease and the natural secretion of glucocorticoids
3		When it is decided to start glucocorticoid treatment, comorbidities and risk factors for adverse events should be evaluated and treated where indicated: these include hypertension, diabetes, peptic ulcer, recent fractures, and presence of cataract or glaucoma, presence of (chronic) infections, dyslipidaemia and comedication with non-steroidal anti-inflammatory drugs
4		For prolonged treatment, the glucocorticoid dosage should be kept to a minimum, and a glucocorticoid taper should be attempted in case of remission of low disease activity; the reasons to continue glucocorticoid therapy should be regularly checked
5		During treatment, patients should be monitored for body weight, blood pressure, peripheral oedema, cardiac insufficiency, serum lipids, blood and/or urine glucose and ocular pressure depending on individual patient’s risk, glucocorticoid dose and duration
6	a	If a patient is started on prednisone not below 7.5 mg daily and continues on prednisone for more than 3 months, calcium and vitamin D supplementation should be prescribed
	b	Antiresorptive therapy with bisphosphonates to reduce the risks of glucocorticoid-induced osteoporosis should be based on risk factors, including bone-mineral density measurement
7		Patients treated with glucocorticoids and concomitant non-steroidal anti-inflammatory drugs should be given appropriate gastro-protective medication, such as proton pump inhibitors or misoprostol, or alternatively switch to a cyclo-oxygenase-2 selective inhibitor
8		All patients on glucocorticoid therapy for longer than 1 month, who will undergo surgery, need perioperative management with adequate glucocorticoid replacement to overcome potential adrenal insufficiency
9		Glucocorticoids during pregnancy have no additional risk for mother and child
10		Children receiving glucocorticoids should be checked regularly for linear growth and considered for growth-hormone replacement in case of growth impairment

tion). Il-4, Il-1β and TNF could not be found at all in the patients with improving morning stiffness. These findings lead the authors to suggest different pathogeneses of RA, one of which being resistant to GCs [27].

After the two weeks of treatment, the mean Il-6 curve maintained its circadian rhythm, but was lower in every time of the day, especially from morning to afternoon. Most remarkable is the missing peak in the early morning hours. Moreover, a statistically significant correlation between the mean 24 h Il-6 concentrations

Table 3
European League Against Rheumatism recommendations on monitoring of adverse events in glucocorticoid therapy (modified according to van der Goes et al., 2010).

	Assessments and feasible methods of monitoring		Minimal monitoring frequency	
Adverse Events	Clinical trials	Daily practice (if different from clinical trials)	Clinical trials	Daily practice
Cardiovascular				
Dyslipidaemia	Blood: fasting lipids	–	Start, end	–
Electrolyte disturbances	Blood: sodium, potassium	–	Start, end	–
Edema	Physical examination: ankle edema	–	Start, end	Start
Hypertension	Blood pressure measurement	–	Start, end	Standard care
Ischemic CVD	1. Questioning 2. Carotid intima-media thickness	Questioning	1. Start, end 2. Start, end	Standard care
Infectious				
Infections	Questioning: occurrence, treatment with antibiotics	–	Start, during follow-up	–
Gastro-intestinal				
Peptic ulcer disease	1. Questioning: complaints 2. Blood: haemoglobin	–	1. Start, end 2. Start, end	Standard care
Psychological				
Mood disturbances	Questioning	–	Start, end	–
Psychosis	Active monitoring not indicated, report of occurrence	–	–	–
Endocrine and metabolic				
Diabetes/ glucose intolerance	Blood: fasting glucose and insulin (HOMA)	Blood: fasting glucose	Start, end	Start, standard care
Body weight and fat redistribution	1. Height 2. Weight 3. Abdominal circumference	1. Height 2. Weight	1. Start, end 2. Start, during follow-up 3. Start, end	Standard care
Interference with hormone secretion	1. Questioning: menstrual disturbances/loss of libido 2. Blood: ACTH stimulation test	–	1. Start, end 2. Start, within 48 h after stopping	–
Dermatological				
Skin atrophy	1. Questioning 2. Sonography for skin thickness (volar part of arm)	–	1. Start, end 2. Start, end	–
Acne, alopecia, bruisability	Questioning	–	Start, end	–
Hirsutism	Questioning	–	Start, end	–
Musculo-sceletal				
Osteoporosis (BMD)	1. DEXA 2. X-rays dorsal spine (if possible) 3. Questioning for fractures	–	1. Start, end (for newly started GCs: also at six months) 2. Start, end 3. Start, end	Standard care according to local guidelines
Osteonecrosis	Active monitoring not indicated; imaging only in case of complaints	–	–	–
Myopathy	Questioning	–	Start, end	–
Ophalmological				
Cataract	Ophthalmologic evaluation	–	Start, end	–
Glaucoma (intra-ocular pressure)	Ophthalmologic evaluation with tonometry	Questioning for risk factors: family history, high myopia, diabetes	Start, end	Start (ophthalmologic evaluation in case of risk factors)

CVD: cardiovascular disease; HOMA: homeostatic model assessment; ACTH: adrenocorticotropic hormone; DEXA: dual-energy X-ray absorptiometry; GC: glucocorticoid.

and the improvement in morning stiffness could be proven. The serum concentration of cortisol showed changes as well after the intervention. Whilst afternoon and evening cortisol values decreased even more, the morning peak continued to rise [27].

The authors conclude that MR-prednisone was capable of reducing RA symptoms significantly at a relatively low-dose. It has not only shown to be able of lowering serum Il-6 levels, but also to provoke an increase in the morning peak of endogenous cortisol, instead of suppressing the hypothalamus-pituitary-adrenal (HPA)-axis, as might have been expected. Hence, it might be possible, that MR-prednisone is able to "improve or correct a deficiency in the HPA control mechanisms", which may be part of RA pathogenesis [27].

Table 4
Glucocorticoid Toxicity Index (modified according to Miloslavsky et al., 2017). Example: a subject of a trial including GC treatment is investigated for glucocorticoid toxicity at the first visit after randomisation. Compared to their values at randomisation, the subject does not show any AEs as listed in the GTI, except for a worsening in blood pressure. Accordingly, their overall GTI Score is 19. Three months later, when GTI is administered the next time, the subject's blood pressure improved (GTI Score: −10), but they developed a moderate increase in BMI (GTI Score: +21). Thus, their current overall GTI Score is 11. If compared to the score of the last GTI administration, which was 19, the subject experienced a reduction of overall GC toxicity. Obviously, alterations in subdomains of the GTI can differ from the overalls trend of the GTI Score.

Composite GTI	Item weight	Specific List
BMI		
Improvement in BMI	−8	Major increase in BMI
No change in BMI	0	
Moderate increase in BMI	21	
Major increase in BMI	36	
Glucose tolerance		
Improvement in glucose tolerance	−8	Diabetic retinopathy
No change in glucose tolerance	0	Diabetic nephropathy
Worsening of glucose tolerance	32	Diabetic neuropathy
Worsening of glucose tolerance despite treatment	44	
Blood pressure		
Improvement in blood pressure	−10	Hypertensive emergency
No change in blood pressure	0	Posterior reversible encephalopathy syndrome
Worsening in blood pressure	19	
Worsening in blood pressure despite treatment	44	
Lipids		
Improvement in lipids	−9	
No change in lipids	0	
Worsening in lipids	10	
Worsening in lipids despite treatment	30	
Bone density		
Improvement in bone density	−1	Major decrease in bone density
No change in bone density	0	Insufficiency fracture
Decrease in bone density	29	
Steroid myopathy		
No steroid myopathy	0	Severe steroid myopathy
Mild steroid myopathy	9	
Moderate steroid myopathy or greater	63	
Skin toxicity		
No skin toxicity	0	Severe skin toxicity
Mild skin toxicity	8	
Moderate skin toxicity or greater	26	
Neuropsychiatric toxicity		
No neuropsychiatric symptoms	0	Psychosis
Mild neuropsychiatric symptoms	11	GC-induced violence
Moderate neuropsychiatric symptoms or greater	74	Other severe neuropsychiatric symptoms
Infection		
No significant infection	0	Grade IV infection
Oral/vaginal candidiasis or uncomplicated zoster	19	Grade V infection
Grade III infection or greater	93	
Endocrine		
		Adrenal insufficiency
Gastro-intestinal		
		Perforation
		Peptic ulcer disease
Musculoskeletal		
		Avascular necrosis
		Tendon rupture
Ocular		
		Central serous retinopathy
		Intraocular pressure elevation
		Posterior subcapsular cataract
Total	-36 to 439	

GTI: Glucocorticoid Toxicity Index; BMI: body mass index; GC: glucocorticoid.

The randomised, double-blind CAPRA-1 study was designed to compare the effects of MR-prednisone to those of conventional, immediate-release prednisone. 288 subjects, who had been taking GCs for at least three months and with morning stiffness of at least 45 minutes, were randomised to receive either MR-prednisone or immediate-release prednisone. The dosage of prednisone was the same each patients received before the trial. While the primary endpoint was the assessment of morning stiffness after twelve weeks of treatment, secondary endpoints were other parameters such as safety, DAS28, ESR or C-reactive protein (CRP). After twelve weeks of treatment, both relative and absolute changes in morning stiffness in the MR-prednisone group compared to baseline were statistically significant (mean absolute change: −43.96 min, mean relative change: −22.7%). The difference between changes in the MR-prednisone group and the control group were significant after weeks 2 and 4 to 12 (Fig. 1). The mean absolute and relative changes in MR-prednisone versus immediate-release prednisone after twelve weeks were -43.96 min versus −22.68 min and −22.7% versus −0.4%, respectively. Except for a significant relative change in Il-6 serum concentration in the MR-prednisone group, no clinically relevant differences between study and control group could be found in secondary outcome measurements. This applies to safety data as well. Although they consider further research necessary, the authors' conclusion is "that modified-release prednisone provides an improvement with respect to conventional glucocorticoids for the treatment of rheumatoid arthritis" [28].

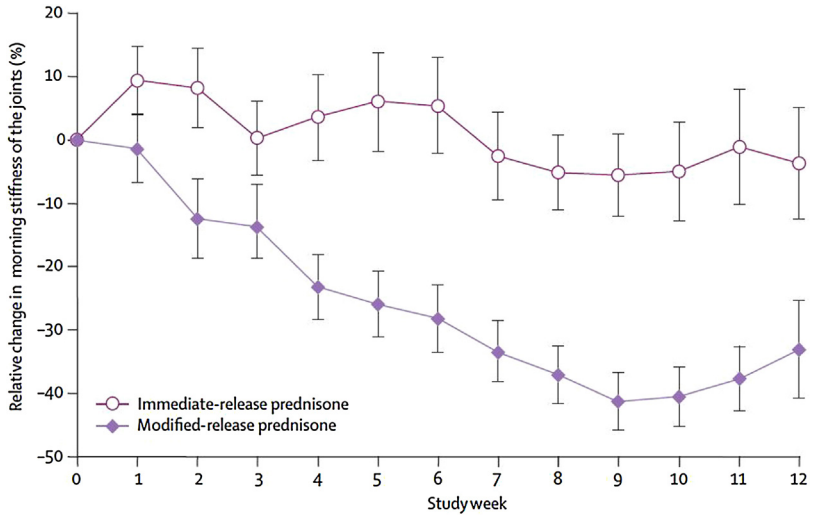

Fig. 1. Morning stiffness changes after start of therapy with immediate-release prednisone and modified-release prednisone in the CAPRA-1 study.

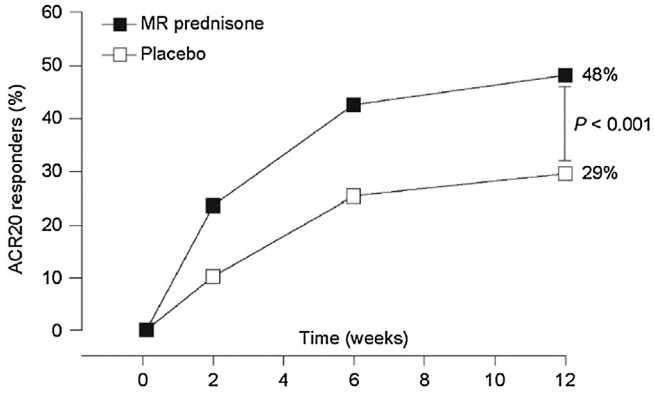

Fig. 2. American College of Rheumatology 20 response rates of modified-release prednisone and placebo group in the CAPRA-2 study. ACR: American College of Rheumatology; MR: modified-release.

A study performed by Alten et al. on HPA-axis function in some subjects of CAPRA-1, who continued MR-prednisone treatment, found no differences in corticotropin-releasing hormone (CRH) testing twelve months after switching from immediate-release prednisone to MR-Prednisone. Therefore, this switch did not contribute to a higher risk of HPA-axis suppression or worsening in pre-existing HPA-axis insufficiency. Furthermore, no AEs relatable to HPA-axis impairment were found in this study, indicating a tolerable safety profile of MR-prednisone, not inferior to immediate-release prednisone [29].

In a further, randomised, double-blind trial (CAPRA-2) patients were randomised 2:1 to receive either 5 mg MR-prednisone or placebo. Patients must have not taken GCs for at least six weeks before screening. After twelve weeks of treatment, the MR-prednisone group revealed significantly higher response rates in ACR20 and ACR50 compared to the placebo group (48% versus 29% and 22% versus 10%) (Fig. 2). Statistically significant differences in favour of MR-Prednisone could also be observed in the changes in tender and swollen joint counts, patient pain and global Score, Physician Global Score, Functional Disability Index of the Health Assessment Questionnaire (HAQ-DI) severity and recurrence of morning stiffness, morning and evening Pain Score, DAS28 Score, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), the physical component of the 36-item Short-Form Health Survey (SF-36) and Il-6 serum concentration. Thus, MR-prednisone proved to be more efficacious than placebo in reducing disease activity, (joint) pain and joint swelling and morning stiffness, while restoring quality of life and physical function. Moreover, incidence of AEs in general and also of AEs considered to be related to treatment as well as for infections was similar in both groups [30]. According to these data, MR-prednisone appears to have an acceptably low risk of harm.

Nevertheless, MR-prednisone is currently available in Germany, Italy, Switzerland and the United States of America only. A certain reluctance in spreading MR-prednisone may at least partially be caused by economic considerations because of its relative expansiveness, if compared to conventional prednisone (which is about 20 times cheaper in Germany and about 350 times in the USA) [31,32]. Despite these differences, MR-prednisone has been calculated to be cost-effective for specific subgroups of RA patient both in the UK and Germany [33,34].

Alternatively, treatment protocols, which split the daily dose of immediate-release prednisone, have been proposed. A study performed by Alten et al. has shown that this protocol does not show any significant difference compared to the once-daily use of conventional, immediate-release prednisone [35,36]. Accordingly, it should not be expected to reduce specific symptoms, such as morning stiffness, as effectively as MR-prednisone.

9. Liposomal glucocorticoids

As described by Strehl et al., also trials on GCs in liposomes, tiny vesicles limited by a phospholipid bilayer, have shown promising results. Animal studies showed either superiority of liposomal GCs to conventional GCs when being used at the same or even a lower dosage. The rationale of these new GC vehicles is avoiding GC occurrence and therefore effects at tissues other than the target, likely leading to a reduction of AEs. First studies in human RA patients have been conducted and their results are eagerly awaited [37].

10. Dissociated agonists of glucocorticoid receptors

Based on the suggestion that on cellular level the genomic effects of GCs can be divided into transactivation and trans repression, of which the first is supposed to be the main cause of adverse events and the latter responsible for most of the anti-inflammatory effects, so-called dissociated agonists of GC receptors (DAGRs) have been developed. Even though this theory appears to be at least partially

refuted [37], a first phase 2 clinical study on PF-04171327 or fosdagrocobat in RA patients revealed auspicious findings. In this study fosdagrocobat 25 mg and 10 mg was found to be more effective in reducing disease activity than placebo. The fosdagrocobat 25 mg group also showed statistically significant larger improvement in disease activity than the prednisone 5 mg group. The numerical difference in disease activity reduction compared to prednisone 5 mg was also in favour of fosdagrocobat 10 mg, but results were not significant. Safety data showed no serious AEs at all and AEs in 8 (38.1%) fosdagrocobat 10 mg patients, 3 (13.6%) fosdagrocobat 25 mg patients, 4 (19%) prednisone 5 mg patients and 12 (54.5%) placebo patients [38]. Although these data look promising, further and in particular larger studies must be undertaken to achieve more distinct data on efficacy and safety.

11. Intramuscular application of glucocorticoids

In the T-REACH study, GCs were used as bridging therapy either orally (as tapering scheme) or intra-muscularly combined with MTX, sulfasalazine and hydroxychloroquine. Efficacy and short-term safety results were similar in both groups [39]. Nevertheless, intra-muscular application might be capable of avoiding some systemic AEs or self-administration of overdoses. Thus, studies focussing mainly on this question might be useful.

12. Conclusion

During their relatively long history, the positive effects of GCs in RA have been well-documented both in short- and long-term treatment. Also, data on some adverse conditions connected to low-dose GC exposure is convincing (hyperglycaemia/Diabetes Mellitus or alterations in BMD). However, at least for some conditions, only trends can be detected, such as for infections and CVD. To gain clarity concerning these issues, further research will be required. Additionally, clearer distinction between AEs caused by GCs and consequences of the disease itself is needed to avoid biases.

As a consequence of the data available, reduction of toxicity must be central in GC therapy. Therefore, it will become necessary to individualise GC treatment based on every single patient's required dosage and their individual risk factors, some of which might make preventive measures inevitable. The GTI is an important development for quantification of GC toxicity and is required for the comparison of diverse GC administrations or regimes. After a further process of validation, it should be crucial for any trial assessing safety of GC therapy. MR-prednisone has shown be as effective as immediate-release prednisone in reduction of disease activity and even more effective in improving morning stiffness, while showing a similar safety profile. Moreover, it appears to be superior to placebo as well. Though these first results need to be confirmed by future trials, with its expected low risk of harm, MR-prednisone might either offer better disease and/or symptoms control than immediate-release prednisone at the same dosage or the same effects at a lower dosage, probably reducing safety risks. Other approaches (such as liposomal GCs or DAGRs) appear auspicious, but further, more detailed research will be needed to evidently assess their worth.

If all of these current developments in reducing glucocorticoid toxicity will prove to be as promising as they appear, glucocorticoids will probably remain a precious part of the treatment of Rheumatoid Arthritis.

Disclosure of interest

The authors declare that they have no competing interest.

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