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REVIEW

# Balancing benefits and risks of glucocorticoids in rheumatic diseases and other inflammatory joint disorders: new insights from emerging data. An expert consensus paper from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)

Cyrus Cooper[1,2] · Thomas Bardin[3] · Maria-Luisa Brandi[4] · Patrice Cacoub[5,6] ·
John Caminis[7] · Roberto Civitelli[8] · Maurizio Cutolo[9] · Willard Dere[10] ·
Jean-Pierre Devogelaer[11] · Adolfo Diez-Perez[12] · Thomas A. Einhorn[13] ·
Patrick Emonts[14] · Olivier Ethgen[15] · John A. Kanis[16] · Jean-Marc Kaufman[17] ·
Tore K. Kvien[18] · Willem F. Lems[19] · Eugene McCloskey[16] · Pierre Miossec[20] ·
Susanne Reiter[21] · Johann Ringe[22] · René Rizzoli[23] · Kenneth Saag[24] ·
Jean-Yves Reginster[25]

## Abstract

*Purpose* This consensus review article considers the question of whether glucocorticoid (GC) therapy is still relevant in the treatment of rheumatic diseases, with a particular focus on rheumatoid arthritis (RA), and whether its side effects can be adequately managed. Recent basic and clinical research on the molecular, cellular and clinical effects of GCs have considerably advanced our knowledge in this field. An overview of the subject seems appropriate. *Methods* This review is the result of a multidisciplinary expert working group, organised by European Society for Clinical and Economic Aspects of Osteoporosis and

✉ Cyrus Cooper
cc@mrc.soton.ac.uk

1 MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK

2 NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, UK

3 Department of Rhumatologie, Hôpital Lariboisière Assistance Publique Hôpitaux de Paris, University Paris VII, Paris, France

4 Department of Internal Medicine, University of Florence, Florence, Italy

5 Department Hospitalo-Universitaire I2B, INSERM, UMR S 959, CNRS 7211, UPMC University of Paris 06, Paris, France

6 Group Hospitalier Pitié-Salpêtrière, Department of Internal Medicine, Paris, France

7 UCB Biosciences, 8010 Arco Corporate Drive, Raleigh, NC, USA

8 Division of Bone and Mineral Diseases, Washington University, St. Louis, MO, USA

9 Research Laboratories and Clinical Academic Division of Rheumatology, University Medical School of Genoa, Genoa, Italy

10 Internal Medicine, University of Utah, Salt Lake City, UT, USA

11 Rheumatology Department, Saint-Luc University Hospital, Louvain University in Brussels, Brussels, Belgium

12 Servicio de Medicina Interna y Enfermedades Infecciosas, Hospital del Mar-IMIM and RETICEF, Barcelona, Spain

13 Department of Orthopaedic Surgery, Boston University Medical Center, Boston, MA, USA

14 Bone and Cartilage Metabolism Unit, Department of Public Health Sciences, University of Liege, Liège, Belgium

15 Department of Public Health, Epidemiology and Health Economics, University of Liège, Liège, Belgium

16 Centre for Metabolic Bone Diseases, Centre for Integrated Research in Musculoskeletal Ageing, University of Sheffield, Sheffield, UK

17 Department of Endocrinology, Ghent University Hospital, Ghent, Belgium

18 Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

19 Department of Rheumatology, VU University Medical Hospital, Amsterdam, The Netherlands

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Osteoarthritis. The recent literature was surveyed and the salient evidence synthetized.

*Results*   The pathophysiological basis of RA (and other inflammatory rheumatic diseases) now strongly implicates the adaptive immune system in addition to innate mechanisms. The molecular effect of GCs and differential GC sensitivity is better understood, although exploiting this knowledge is still in its infancy. The newer treatment strategies of early and aggressive control of RA have greatly improved clinical outcomes, but improvements are still possible. Newer targeted anti-inflammatory drugs have made an important impact, yet they too are associated with numerous side effects.

*Discussion*   Short durations of moderate doses of GCs are generally well tolerated and have a positive benefit/risk ratio. Patients should be assessed for fracture risk and bone preserving agents and be prescribed calcium and vitamin D supplementation.

*Conclusions*   Within a strategy of a disease modifying approach to inflammatory disease, combination therapy including a GC is effective approach.

**Keywords**  Rheumatoid arthritis · Rheumatic diseases · Osteoporosis · Cohort studies · Glucocorticoids · Inflammation

## Introduction

The decade of the human genome (2000–2010) [1] brought in a number of significant advances to the understanding of pathophysiology of rheumatoid arthritis (RA); not only the genetic components of the disease, but also the involvement of activating environmental factors and the subsequent immune response. That decade also bore witness to a number of clinical advances in the treatment of RA, forged out of the collaborative efforts of American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) to standardise the clinical approach and from the fresh insights from innovative trials that gave

rise to the ideas of the "window of opportunity" in early RA, and the "tight control", or treat-to-target, which is necessary to optimise the remission rate [2–4]. Glucocorticoid (GC) therapy, which is increasingly associated with greater risks of adverse outcomes, particularly osteoporotic fractures, has been omitted from some treatment guidelines, but some experts have remained convinced of its value in rapidly controlling the inflammation in the joints. In parallel with these developments, that decade saw the launch of several biological disease-modifying agents (biological DMARDs) which have made an important impact in managing immunoinflammatory diseases.

The clinical management of rheumatic diseases is a very active research field and effects of GC therapy continue to provoke much debate. What are the risks and how does GC therapy measure up to newer treatment strategies with biological DMARDs and can GCs be incorporated in these strategies? Can we consider the risks associated with GCs, in both muscles and bone, as well as in other organ systems as manageable? Could the stratification of patients according to their risk of developing side effects from using GC's optimise benefit?

Such were the questions at a recent expert working group of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) convened to discuss the current evidence for and against the use of GC's in rheumatic diseases. With a focus on RA, this review attempts to put into perspective the progression of our knowledge of the adverse effects of GCs (within the limits of our appreciation of cause and effect) with the advances in our understanding of the inflammatory response.

## New insights into the pathophysiological basis of RA

The pathogenesis of RA has been well described by Klareskog and colleagues in an excellent review, so only a few salient points will be described here. Because of the multiplicity of interacting factors that give rise to this clinical condition, they describe RA as a "complex genetic disease" [5].

It is now clear that neutrophil-dominated inflammation (an innate immune response) plays an important role in RA, as is also the case for inflammatory pulmonary diseases such as asthma, chronic obstructive pulmonary disease (COPD), bronchiolitis and cystic fibrosis [6]. This similarity seems pertinent since early manifestations of RA are frequently in the lung [7]. Indeed, smoking and other forms of pulmonary insult increase the risk of RA, especially in persons with specific genetic modifications at the human leukocyte antigen (HLA) gene, thus giving rise to

[20]  Immunogenomics and Inflammation Research Unit, Department of Immunology and Rheumatology, University of Lyon 1, Lyon, France

[21]  Bonn, Germany

[22]  West German Osteoporosis Center (WOC), University of Cologne, Leverkusen, Germany

[23]  Service of Bone Diseases, Faculty of Medicine, Geneva University Hospitals, Geneva, Switzerland

[24]  Division of Clinical Immunology and Rheumatology, University of Alabama, Birmingham, AL, USA

[25]  Department of Public Health, Epidemiology and Health Economics, University of Liege, Liège, Belgium
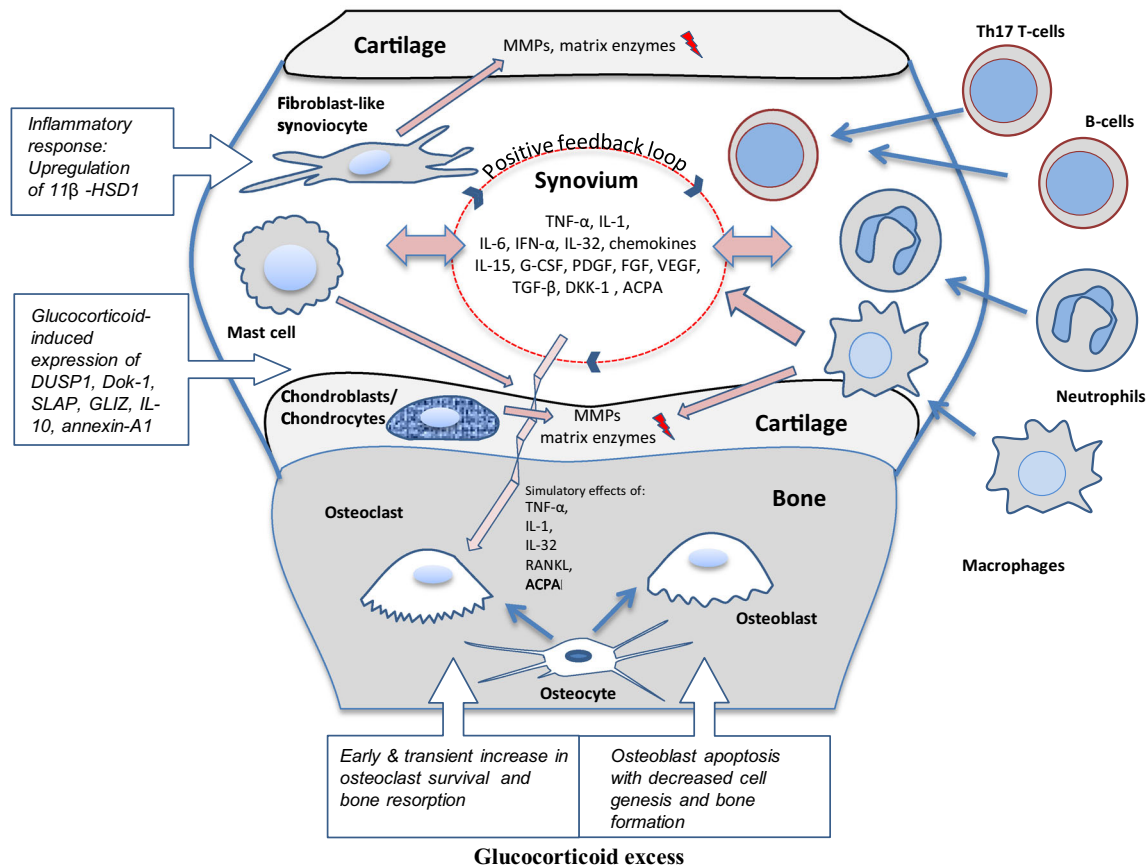
**Fig. 1** Cellular interactions within the joint in rheumatoid arthritis. In the symptomatic phase of the disease, cells from the innate immune system located in the synovium, including mast cells, neutrophils and macrophages, respond to stimulation by ACPA-immune complexes and/or rheumatoid factor and/or other triggering factors, by the release of cytokines and chemokines. The chemokines attract activated cells of the adaptive immune system (T- and B-cells) which invade the synovium and start to secrete inflammatory cytokines (*line arrows* indicate the movement of cell types; *square arrows* link the sources and targets). A positive feedback loop involving cytokines, prostaglandins, reactive oxygen intermediates and trophic factors ensues (only a few of the implicated signalling molecules are illustrated), marshalling immune cells, synovial fibroblasts, chondrocytes, and osteoclasts. This, together with the release of matrix proteases and the molecular products of damage, drives the chronic phase of rheumatoid arthritis pathogenesis. Note that endogenous glucocorticoid signalling is locally enhanced via the upregulation of 11β-HSD1 production in most cells. The main inflammatory signals in the synovium include tumor necrosis factor α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6) and interferon-α (IFN-α). Important stimulators of immune cell activation/proliferation include interleukin-15 (IL-15) and granulocyte colony-stimulating factor (G-CSF), while the stimulators of mesenchymal cell proliferation/differentiation are mainly platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF). Other secreted entities are the matrix metalloproteinases (MMPs), transforming growth factor β (TGF-β), dickkopf-1 (DKK-1) and the receptor activator of nuclear factor κB ligand (RANKL). In the adjacent bone, the differentiation of osteoclasts is stimulated by the increased production of RANKL and IL-32. RANKL also stimulates the activity and therefore bone resorption of these cells. The expression of DKK-1, an inhibitor of wnt signalling is also believed to contribute to bone remodelling. References: McInnes et al. [8]; Klareskog et al. [5]; Weinstein [160]; Clark [171]

altered patterns of citrullination of mucosal proteins and other barrier tissues and subsequently antibodies to those entities [5, 8].

The adaptive immune system is also strongly implicated and is now considered to be a key driver of the disease process. Of particular importance is the involvement of the Th17 T-cells (Fig. 1), which become activated to secrete interleukin-17 (IL-17) and migrate along with neutrophils into the synovium. Once there, they induce the local mesenchymal cells to produce proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNFα), a variety of growth factors, and matrix metalloproteinases, with resulting damage to the joint and bone (see [9]). The neutrophils survive for an extended time in the synovium because of the upregulation of a transcription factor that inhibits a regulatory apoptotic pathway [10, 11]. Much effort is now focussed on trying to re-activate apoptosis or otherwise down-regulate inflammatory T cell activity.

The adaptive immune system is also invoked to produce antibodies against rheumatoid factor (RF) and/or against cyclic citrullinated peptides [anti-CCP; also known as

antibodies to citrullinated protein antigens (ACPA)]. The plasma levels of these antibodies give important clues as to the activity of the disease [12, 13]. Higher levels of these antibodies are associated with an increased risk of joint damage and cardiovascular diseases [14]. Whilst the effect of these antibodies in the disease process is not fully understood, recent work has shown that ACPA can stimulate osteoclast differentiation and that in pre-RA individuals, those who are ACPA-positive, there is more frequent evidence of bone loss and reductions in cortical thickness as compared with ACPA-negative individuals [15]. The production of these antibodies is associated with more generalised inflammation, as indicated by higher levels of C-reactive protein (CRP) and higher erythrocyte sedimentation rates [16]. Evidence supports that the presence of ACPA as a better diagnostic test than anti-RF for the disease in asymptomatic individuals [5], however, 20 % of patients with RA (even when well established), are negative for one or other (or both) of these antibodies [13]. The development of ACPA is largely dependent on environmental factors and lifestyle, rather than genetics, while genetic factors have a relatively important effect in determining which ACPA-positive individuals will go on to develop RA [17].

## The impact of RA on organ systems

Epidemiological research in the 1970s and 1980s showed that morbidity and mortality in patients with RA were much higher than in the general population [18]. The possible reasons for this seem to be related to increased cardiovascular (CV) risk, but the contribution of RA to the overall risk profile has proved difficult to determine. Indeed this patient population tends to show high CV risk factor profile, where smoking, hypertension, obesity and diabetes are frequent. This situation created a strong possibility of confounding in the epidemiological studies that was not always adequately controlled and still gives rise to uncertainty. We will therefore provide a brief description of this risk profile of RA patients before discussing the possible contribution of the disease in organ failure.

Smoking is the strongest environmental risk factor for RA and the prevalence of cigarette smoking tends to be higher in RA. In a 2011 meta-analysis of 15 case–control studies (2956 patients and 3713 controls), Boyer et al. found that the prevalence of smoking in RA patients was 56 % higher than in the case controls [odds ratio (OR) 1.56; 95 % confidence interval (CI) 1.34–1.80] [19]. Cigarette smoking has also been associated with increased severity of RA particularly in men with seropositive disease [20]. Hypertension may be more prevalent in this RA patients, with some researchers reporting rates of 50 %

[21]. However, in the Boyer et al. meta-analysis, no clear increase was demonstrated. A tendency towards hypertension is plausible in this population, since several studies have reported an increase in arterial wall stiffness in RA patients (see [22]). The relationship between corpulence and RA risk has been investigated in several studies, but the correlation between BMI and RA remains uncertain [23]. What seems to be more relevant is relative body composition, where increased body fat and reduced muscle mass leads to a condition known as rheumatoid cachexia [23]. Increased central adiposity is common in RA, which in itself is a risk factor for insulin resistance and endothelial dysfunction and could also play a role in RA. An increased prevalence of insulin resistance has been reported in individuals with RA, associates particularly with those having high-grade inflammation [22]. While the association between RA and diabetes mellitus is widely debated, the Boyer et al. meta-analysis did find that the prevalence of diabetes mellitus was significantly increased in RA as compared to controls with an odds ratio of 1.74 (95 % CI 1.22–2.50) ($P = 0.003$) [19]. The COMORA study has highlighted other important comorbidities in RA (that are highly variable between countries) including depression and asthma [24].

## Adverse effects of RA on cardiovascular outcomes

RA patients have a higher CV risk than in the general population [25–27], a risk which is comparable to that of patients with type-2 diabetes [28]. According to one prospective cohort study the age- and sex-adjusted hazard ratio for CV disease was 1.94 versus the general population [28] and in a 2012 meta-analysis of 41,490 patients in observational studies, the patients with RA had a 48 % increased risk of CV disease [i.e. a pooled RR (relative risk) of 1.48, 95 % CI 1.36–1.62] with the risks of myocardial infarction and cerebrovascular accidents increased by 68 and 41 % [29].

It has been expected that the improvements in RA treatment since the 1990's would be reflected by a decrease on annualised CV risk. Initially this hypothesis seemed to be supported by data from the North American ARAMIS registry [30], but other results were conflicting [31]. Additional important confounding factors that were perhaps not fully considered at the time were the drug-related deaths in association with the use of rofecoxib, a specific COX-2 inhibitor, and rosiglitazone, an anti-diabetic drug in the thiazolidinedione class of drugs. Both of these were approved in 1999 (USA), but rofecoxib was withdrawn in 2004 and rosiglitazone, which remains on the US market, was withdrawn from the European market in 2010. Both drugs have been associated with higher rates of MI [32, 33]. It might also be reminded that the non-steroidal anti-

inflammatories, as a drug class, are also not without risk. In a recent network meta-analysis of 31 trials (116,429 patients) [34], ibuprofen and diclofenac (versus placebo) were associated with increased risk of stroke; and etoricoxib and diclofenac were associated with increased risk of CV death. Naproxen appeared to be the least harmful.

A key factor in the increased CV risk, particularly atherosclerosis, is the alterations in circulating lipid profiles seen with RA and other systemic inflammatory conditions [35, 36]. Indeed, a significant proportion of patients diagnosed with RA (and without cardiovascular disease) are reported to have lipid profiles that would mandate statin therapy [37, 38]. Interestingly, some of the RA susceptibility genes seem to be involved in the regulation of lipid metabolism [39]. The risk of incident CV events in RA, however, is not strongly correlated with traditional CV risk factors [22, 40], but more closely associated with inflammation, the extra-articular manifestations of RA [41] and the presence of anti-CCP antibodies [14]. In vitro experiments have shown that IL-17 and TNFα provoke endothelial cells to produce pro-coagulant and pro-thrombotic factors that could change the underlying CV risk [42] and that these effect can be inhibited by simvastatin [43]. A statin therapy in RA patients has also been shown to reduce inflammatory biomarkers and improve the disease activity score (DAS-28) [44].

Indeed, chronic systemic inflammation and changes in lipid metabolism are tightly linked, influencing each other, as well as immune responses. Metabolic "fingerprints" of lipid profiles are distinctive of underlying inflammation and in patients with RA it would seem that this fingerprint is different depending on whether the disease is early or established [45]. Effective RA therapy (defined as at least a 20 % improvement in symptoms), has been associated with "amelioration" in the lipid profile (increased HDL-cholesterol and apolipoprotein A1 levels, but unchanged LDL-cholesterol levels) which could improve CV risk [46]. The relationship between chronic inflammation and CV disease may become clearer with the termination of two clinical studies currently underway: the Cardiovascular Inflammation Reduction Trial testing MTX 15–20 mg in coronary patients (estimated completion date: December 2018) and the Novartis trial of canakinumab, a monoclonal antibody directed against IL-1β, in post-MI patients (estimated completion date: July 2016).

Also associated with RA is an increased risk of stroke, particularly ischemic stroke, which is correlated with RA severity, cardiovascular risk factors and comorbidity [47].

### Adverse effects of RA on bone health

The destruction of cartilage and bone are major effects of RA [5, 8]. The activation of matrix metalloproteases is the main driver of the degradation of cartilage, although other processes contribute. In the bone, the increased expression of the "receptor activator of nuclear factor κB ligand" (RANKL) and the expression of osteoprotegerin, results in enhanced promotion of osteoclast differentiation and subsequent bone loss (see [9] for references). The erosion tends to occur at sites subjected to mechanical stress or loading, thus the periarticular, cortical sites are more vulnerable. Also, as stated above, recent evidence suggests that ACPA can directly stimulate this process via enhanced osteoclast differentiation [15].

### Adverse effects of RA on the immune system

Patients with RA have a greater risk of infection than matched controls [48]. This may be due to a combination of factors including the immunomodulatory effects of RA, smoking, increasingly sedentary lifestyle and the effect of drugs used in RA treatment. However, the chronic systemic inflammation in RA also seems to induce a defect in the immune response via an effect on T helper cells [49]. The short-term administration of low-doses of GC has a beneficial effect on this defect (Miossec, personal communication).

### GC therapeutic strategies in RA

In the early 1990s, the first-line treatment for RA was nonsteroidal anti-inflammatory drugs (NSAIDs). GC therapy was mostly as a second-line with varying strategies of step-down, step-up or pulse dosing. The clinical efficacy of GCs was considered as limited since the beneficial effects ended rapidly after treatment withdrawal. Other second-line therapies in RA, such as methotrexate (MTX) and sulfasalazine (SSZ), were beginning to be recognised as having good effectiveness profiles [50], especially when administered in combination [51].

In 1997, the COBRA trial results revealed the possibilities of a different strategy [52]: the treatment newly diagnosed (early) RA with a combination of SSZ and MTX, plus high doses of prednisolone in a step-down regimen. In this randomised study with a blinded outcome assessment (disease activity score and radiographic damage score), the GC arm showed a higher rate of improvement at week 28 than with SSZ alone (72 versus 49 % of patients improved according to ACR criteria. This study and a number of important clinical studies that followed in the period 1999–2013 (one could mention: Fin-RACo [53], BARFOT [54], TICORA [3], BeSt [55], CAMERA-II [56], DREAM [57] IMPROVED [58] and COBRA-light [59]) helped build on the idea that there was a "window of opportunity" in early RA and that tight control the

inflammation or "treating-to-target" (i.e. remission or minimal disease activity) resulted in better long-term outcomes.

Several systematic reviews have concluded that low dose (≤7.5 mg/day) GC can provide a useful "bridging-therapy" below the therapeutic effects of the slower acting DMARDs start to manifest [60–63]. Conclusion accepted by EULAR in their 2010 recommendations [64] and further confirmed in 2014 [65]. The ACR has been rather more reticent on the use of GCs and in its 2012 update of recommendations, focussed on conventional DMARDs and biological therapies and did not address the use of GCs [66].

## The risks of GC therapies

The most commonly self-reported adverse events by patients who are prescribed with longer-term GC use are weight gain (about 70 % of individuals), skin bruising (∼55 %), sleeping problems (∼45 %) and mood problems (∼45 %) and all show a positive relationship with GC exposure [67]. It might be added that a constructive patient-practitioner dialogue at the start of any GC therapy is very important [68]. The adverse reactions associated with GC therapy have been described in more detail in recent reviews [69, 70]. From a clinical aspect, the more serious adverse reactions are outlined below.

### Adverse effects of GCs on bone health and fracture: epidemiology

In the early 1990s, it was clear that GCs could negatively impact bone health, but the magnitude of effect was unclear. Confirmation of a bone demineralising effect of GC therapy accrued gradually throughout the 1990s with the publication of a review with meta-analysis [71] and with the very large cohort analyses of the UK's GPRD database by van Staa et al. [72, 73]. The latter group demonstrated that patients exposed to GCs had higher relative risk of fracture (versus age-matched non-exposed individuals), with relative risk ratios varying from 1.1 for forearm fracture, through 1.6 for hip, to 2.6 for vertebral fracture. Again, one of the major difficulties encountered in observational studies, is controlling for confounding factors, since the decision to prescribe a GC (and the dose selection) is greatly influenced by the activity of the underlying disease and the age of the patient. The rate of bone loss will vary also according to these factors, as well as others (patient sex, baseline BMD, previous fracture history) [74].

The effects of GC on fracture risk are not only dose-related effect, but dependent on an integration of daily dose and duration of exposure. The cumulative dose per patient was found to be pertinent metric in a case-controlled study by Vestergaard et al. on a Danish registry [75]. This study a slight increase in hip fracture risk for patients who received 130–499 mg (OR 1.17), a higher risk for patients at 500–1499 mg (OR 1.36) and the greatest risk for patients at levels of 1500 mg or higher (OR 1.65). Van Staa and colleagues, in contrast, in their post hoc analysis of two prospective studies testing bisphosphonate efficacy in postmenopausal GC users [76], reported that daily GC dose (and not cumulative) was the stronger predictor of vertebral fracture risk compared with nonusers. This issue is not resolved, but with short treatment durations, the daily dose seems to be the key risk factor, but with longer durations (>3 months) and without any high dose administration, it would seem that cumulative dose is more important. This "exposure integral" further complicates the identification of a threshold above which adverse effects become more likely.

In a meta-analysis published in 2004 of the findings from seven prospective cohorts (42,500 individuals) Kanis and colleagues [77] also came to the conclusion that GC exposure increases the risk of any fracture, osteoporotic fracture and hip fracture. This increase in risk was only partly explained by a decrease in BMD, suggesting that bone remodelling induced by GC exposure weakens bone more than is indicated by the change in BMD [77]. Such remodelling could be fairly localised and not easily observed in standard DXA scans. It has, for instance, been argued that a lateral subregional approach to areal BMD measurement can show relevant BMD loss in GC exposed individuals which is masked in the standard posterior-anterior projection [78]. Trabecular thinning appears to be an important consequence of GC therapy and contributory to the increased bone fragility [79–81]. The recently developed trabecular bone score may find a role in the assessment of fracture risk in GC treatment [82].

### GCs effects on bone: pathophysiology

The pathophysiological effects of GC on bone metabolism appear relatively rapidly after initiation of treatment with GC. In a pioneering study in 1995, Lems et al. [83] showed that the levels of serum osteocalcin (markers of bone formation) in healthy male volunteers decreased significantly with exposure to 10 mg prednisone per day for 1 week. A finding that was later confirmed in a larger study of healthy postmenopausal women [84]. Both studies observed that, whereas markers of bone formation were reduced during treatment, the markers of bone resorption were relatively unchanged. Both furthermore showed that the levels of bone formation markers rebounded back to pre-treatment levels after the end of treatment.

Serious bone problems remain uncommon, but association of higher GC exposure with osteonecrosis was described in an analysis of 71 patients with severe acute respiratory syndrome (SARS) who were treated with high doses of GCs [85]. Ten percent of the cohort developed radiographic evidence of osteonecrosis and they had received total GC doses >2.5 g prednisolone equivalents and treatment duration exceeding 18 days. The assessment of bone biomarkers, early during treatment and at repeated intervals, did not indicate any predictive pattern in those patients who went on to develop osteonecrosis. In orthopaedic clinics, it is estimated that about 15 % of the hip replacements are due to osteonecrosis and about half of those are associated with GC use (Einhorn, personal communication). Possible risk factors for osteonecrosis are considered to be related to the vasculature and blood clotting (there is an increased risk in lupus), but also lipid intermediaries and the presence of anti-phospholipid antibodies. It is of considerable interest in this respect, the recent discovery of specialised endothelial cells within bone which directly stimulate osteoprogenitor cells [86, 87]. The possibility is also raised therein of a novel method to stimulate the regeneration of osteoblasts.

### GCs effects on bone: counteracting bone loss

The risk of GC-induced osteoporosis became a major concern in the late 1990s, especially in persons older than 70 years, [88, 89], and physicians were encouraged to prescribe bone preserving agents. Widely prescribed were the bisphosphonates [90, 91], as well as calcium and vitamin D supplementation [92]. The combination of bisphosphonates with GC and a DMARD can protect against bone loss and may even increase BMD in the lumbar region [93]. The evidence of long-term safety of bisphosphonates in GC-users is sparse [94] and it may be that patients should be switched to a different bone-preserving agent after 2 years since their continued use may be associated with low bone turnover and atypical fractures [95]. The data from the longitudinal GLOW study (in postmenopausal women) [96] would suggest that management of bone health for GC-users is however far from optimal. BMD testing is more frequent in GC users than non-GC users and their awareness of osteoporosis risk is better, but their treatments, even calcium and vitamin D supplementation remain inadequate; especially in Europe.

### Adverse effects of GCs on the cardiovascular outcomes

Since systemic inflammatory diseases increase CV risk, the evaluation of the added effect of GC treatment is complicated. In general, GC therapy has been charged with tipping the balance further to the side of harm [97, 98], which is understandable given that long-term GC therapy use has been associated with hyperlipidaemia [99], hyperglycaemia [100], increased body mass, blood pressure and cholesterol [101]; all known CV risk factors. The evidence however has mostly been indirect. Wolfe and colleagues noted that the strongest explanatory factor for the increased MI risk in patients with RA was the activity of the disease itself and the patients with overt RA were more likely to be treated with a GC. Since there was evidence to link GC use with the increased risks for diabetes and hypertension, confounding likely accounted for the observed association between GC use and the overall risk of MI [102]. It remains possible however that some interaction exists between RF-positivity and exposure to glucocorticoids in the risk of CV events [103]. Longer-term GC use in the medium dose range in patients with RA has been linked with hypertension [104] and it may also increase the risk of venous thromboembolism [105].

### Adverse effects of GCs on the immune system

High endogenous GC secretion (hypersecretion), as well as high exogenous GC doses have been associated with lung infections and opportunistic fungal infections [106]. In a nested case–controlled analysis using data from a Canadian administrative database, a 2011 publication [107] reported that there was a dose response in the prevalence of serious infection in older patients with RA according to GC use (cumulative dose weighted by the closeness in time to the index date, i.e. diagnosis of infection). The odds ratio for current GC exposure (at 5 mg prednisolone/day) was 1.5 and the risk was found to increase with the duration of treatment (comparative groups: 3, 6 months and 3 years). The immune function recovered following GC withdrawal, but relatively slowly. Thus discontinuation of a 2-year course of 10 mg prednisolone halved the risk as compared to on-going use, 6 months later, but the cumulative exposure still appeared to have an impact on current risk [108]. A retrospective analysis published in 2006 [109] reported that RA patients who received low-dose GC therapy for more than 10 years had increased mortality compared to those who did not receive GCs and that this increased mortality was mainly due to infections and complications related to systemic amyloidosis.

Once again, determining the relationship between GC dose and additional risk of opportunist infections is not an easy task. The observational studies are often compromised by confounding by disease severity, intermittent patterns of GC use and administration route; controlled interventional trials by heterogeneous reporting and publication bias [110]. A recent systematic review of serious infection with biological treatments for RA concluded that an increase in risk exist with respect to traditional DMARDs but put the

absolute risk of infection with a standard dose regimen at 6 per 1000 [111].

### Effects of GCs on glycaemia

The hypothalamic-pituitary-adrenal (HPA) axis is closely implicated in the regulation of adipose tissue and metabolic pathways [112, 113] and studies have shown that glucocorticoids induce hyperglycaemia and may cause diabetes or aggravate pre-existing diabetes [114, 115]. The mechanisms underlying the effect remain poorly understood, but appear to include increases in gluconeogenesis and hepatic glucose output, as well as inducing insulin resistance [116]. In a cross-sectional analysis of patients with established RA and without type 2 diabetes mellitus, tests showed that there was no difference between chronic GC users and GC-naïve patients in terms of glucose tolerance, insulin sensitivity and β-cell function [117]. As already described, RA patients tend to have decreased insulin sensitivity and impaired β-cell function when compared to control subjects of comparable age with normal glucose tolerance. Low doses of prednisolone have been shown to acutely affect carbohydrate metabolism [117] and GC-induced hyperglycemia is common in individuals with or without diabetes [114]. However, within the context of RA, the long-term effects of low-dose GC are not clear and longitudinal studies are required in this area. Short-term high dose GC treatment (30 or 60 mg/day), seems to have a variable effect on glucose metabolism with some patients showing improvements and others deterioration [118]. In a cross-sectional analysis of the NHANES III population of individuals aged 60 years or more ($n = 5302$), the prevalence of diabetes in individuals with RA was 17 % and the estimated increase in the risk of DM associated with RA (adjusted odds ratio of 1.3) had a 95 % CI that spanned 1 and therefore did not reach statistical significance [119].

### Effects of GCs on weight gain

The question of weight gain with GC treatment was examined in a sub-study of CAMERA-II, which compared a combination therapy for RA (prednisone 10 mg/day + MTX) versus MTX alone [120]. The study team found a moderate weight increase in the GC group (mean +2.9 versus +1.3 kg), but no independent association of a change in BMI. A risk of developing metabolic syndrome, on the other hand, does not appear to be associated with GC therapy [121]. While some research has suggested that the synthetic prednisolone derivative, deflazacort, has a more moderate effect on glycaemia than prednisone, this seems to be related to its lower (∼80 %) therapeutic potency [122, 123]. Further work in this field is probably needed to identify the individual risk factors

associated with clinically relevant metabolic effects of low dose GC therapy [124].

### Effects of GCs on vision

Prolonged use of glucocorticoids is a significant risk factor for the development of cataract [125]. The mechanisms underlying the effect remains unknown, but may be linked to gene transcription events in lens epithelial cells [126]. Other risk factors for these typically posterior subcapsular cataracts include age, male gender, diabetes, increased weight change and thyroid hormone use [127].

### Effects of GCs on depression

Cortisol has a complex role in depression and higher levels are a risk factor for depression [128]. The circadian pattern of GC release also seems to be important and the constant levels of an exogenous GC seem to disturb some individuals. Depression is highly prevalent in patients with RA with rates of major depressive disorder, according to a recent meta-analysis [129] of 17 % (95 % CI 10–24 %), which is similar to the 15 % prevalence reported in the COMORA study [24]. According to some self-reported scales however the presence of depressive symptoms may affect 35–40 % of individuals [129]. The presence of depression has been found to reduce the effect of prednisolone treatment by as much as 50 % (on DAS-28 and HAQ scores) [130].

## Optimising the GC response

### The timing of GC administration

Modified release preparations of prednisone, which allow the higher levels of GCs to be attained during the night and therefore simulate the endogenous pattern of cortisol release, could provide superior results than traditional formulations. The loss of the endogenous cortisol rhythm is particularly associated with sleep disturbance, depression, and metabolic abnormalities [128, 133–135]. So far the studies with these compounds have been short-term (3–4 months) with low doses (5 mg/day), but the results seem to be encouraging.

### The choice of administration route

By far the most clinical research into the efficacy and safety of GC therapy in rheumatic diseases has been on orally administered doses. Other routes are associated with local adverse side effects of a more restricted nature:

- Intraarticular administration of GCs on systemic bone metabolism are considered relatively benign, or at least have less adverse effects than systemic oral GC use [136], however high quality randomised trials that actively assess joint damage or fracture risk over time are very rare. One randomised study which did use this strategy was TICORA [3] and no adverse events relating to these injections were described. Some physicians are somewhat less concerned by cartilage damage, since that consider this treatment effective only to postpone an inevitable joint replacement, but the results of TICORA and more recently OPERA [137] would suggest that this approach deserves greater attention. OPERA used a treat-to-target strategy of methotrexate (20 mg/week) and triamcinolone hexacetonide (20 mg/mL, 0.5–2 mL/joint), with or without an additional biologic DMARD. At 6-monthly intervals over 1 year, a maximum four swollen joints per patient were injected with; equivalent to (according to the authors) about 1 mg prednisolone a day during the 12-months' follow-up. The blinded MRI outcome assessment (synovitis, osteitis and tenosynovitis scores, bone erosion and joint-space narrowing) revealed a significant decrease in disease activity and the absence of further bone erosion or structural damage. The addition of a biologic DMARD (adalimumab) gave better results on the tenosynovitis and osteitis scores than without.
- Topical GCs are known to have various degrees of systemic exposure but rarely have consequential effects on bone [138, 139].

### The choice of GC formulation

There are distinct differences between GC formulations in the residence time in the joint, which can vary from ∼2.8 days for methylprednisolone and betamethasone, ∼4 days for triamcinolone acetonide, 6 days for triamcinolone hexacetonide and 25 days for rimexolone [140, 141]. Triamcinolone hexacetonide was the preferred choice in a recent review [142] based on clinical response. For the treatment of adhesive capsulitis a 20 mg dose of triamcinolone hexacetonide was recently been demonstrated to be non-inferior to a 40 mg dose, so it is possible that similar dose comparisons might prove valuable in RA [143]. Further long-term safety studies are also warranted since fluorinated glucocorticoid preparations, such as triamcinolone, may be more strongly associated with myopathy [144].

The expectation has been held for some time that chemical modification could provide GCs with significantly better benefit-risk ratios [145–147] but so far these remain elusive. Thus, the nitrosteroids and the selective glucocorticoid-receptor agonists (SEGRAs) or dissociating glucocorticoids have, as yet, failed to "sharpen the old spear."

The bioavailability of GC is regulated by several different mechanisms. A large portion of the circulating GCs is bound to corticosteroid-binding globulin and serum albumin. GCs are also metabolised in the circulation and may be reactivated in certain tissues by the enzyme 11-beta hydroxysteroid dehydrogenase (11β-HSD, type 1; expressed in brain, bone, synovium, liver and adipose tissue), which catalyses the conversion of (inactive) cortisone to cortisol thus modulating the local bioavailability of active GC.

### GC resistance

GC resistance is a fairly well documented phenomenon in respiratory diseases such as asthma, but comparatively less so in other chronic inflammatory conditions [148]. The result of this "resistance" is that relatively high doses are necessary before an anti-inflammatory effect is seen [148, 149] and to some degree this physiological dysregulation is probably responsible for a high basal immune activation state. The prevalence of GC resistance is difficult to measure since several different definitions exist, but it is estimated that about 30 % of patients with RA have a poor clinical response to glucocorticoids [112, 150]. Various treatment are being explored to reverse acquired GC resistance [151].

Genetic polymorphisms of the GC receptor is one reason for GC resistance and this may play a role in RA [152, 153]. Acquired GC resistance may also be a factor in GC resistance and the oxidative stress caused by smoking is also associated with a reduction in the anti-inflammatory effects of GCs in respiratory disease [148]. Chronic stress is known to have a marked (central) effect on the hypothalamic-pituitary-gonadal axis—a result well known to behaviorists [154]—and such a mechanism has not been entirely ruled out in RA [155, 156]. Indeed it has been argued that to understand the development of chronic inflammatory diseases, a complete workup of the hypothalamic-pituitary-gonadal axis as well as the hypothalamic-pituitary-adrenal axis is required. Imbalances within these complex systems and their interactions with the immune system could be crucial in the development of such diseases and their response to treatment [157].

## Current treatments for RA

### Use of GCs

The subject of glucocorticoid-induced osteoporosis was addressed in two consensus statements on [158, 159],

which seemed to agree that two important steps in GC discussion are a daily dose ≤7.5/>7.5 mg/day prednisone and a treatment duration <3/≥3 months. Differences persist however in the thresholds above which anti-osteoporosis drugs should be described [160]. A framework for treatment management decisions for GC-induced osteoporosis in patients whose therapy last for 3 months or longer has recently been proposed [161]. EULAR has published recommendations for monitoring for potential side-effects of systemic GC therapy in rheumatic diseases [162] and for the management of medium to high GC doses (i.e. >7.5 and ≤ 100 mg prednisone equivalent daily) [163], which could help to lay the foundations of a stratification procedure for the use of GC in patients with RA.

### GC-withdrawal

GC-withdrawal has been fairly recently recognised as serious problem where there is long-lasting suppression in the functioning of the HPA axis [131]. The symptoms seem to be quite varied and include vomiting, abdominal pain, weakness, malaise, fever, hypotension, hypoglycaemia, and hypernatremia. The discontinuation of long-term GC therapy has also been associated with an increased risk of both depression and delirium/confusion [132]. More research and awareness are needed on this issue, particularly in elderly, and to understand how this is related to the recovery of trabecular bone density.

### Special considerations for GC therapy in older patients

Fracture risk should be estimated (FRAX score or other tool) and, depending on risk score and access to densitometry, a BMD measurement at the level of the lumbar vertebrae and femoral neck [164]. In post-menopausal women and at-risk men, the biomarkers of bone metabolism may be helpful for determining therapeutic strategy with the prescription of bone sparing treatments [165] and for this it should be noted that blood sampling is best performed in the morning in adequately hydrated patients in a fasting condition. Appropriate regimens of supplementation with calcium and vitamin D are usually warranted [92] although it is cautioned that upper thresholds are not exceeded (2000 mg/day calcium (diet + supplement); 800–1000 IU/day vitamin D). It should also be noted that vitamin D deficiency has been associated with various autoimmune diseases including RA and lupus [166].

CV risk is known to increase with age [167] and, as we have seen systemic immune disease further increases this risk. It is important therefore to submit patients to a thorough CV risk assessment prior to initiating therapy with GC's. Any hyperglycaemia, hypertension or dyslipidaemia should be managed as much as possible before prescribing a GC. Traditional CV risk factors and RA-associated risk differ, but recent work shows how an existing risk score might be adjusted in the context of RA [168], integrating disease activity, disability, daily prednisone use (yes/no), and disease duration (less than 10 or 10 years or more).

Additional baseline assessments should also be made of ankle oedema and risk factors for glaucoma [169].

### Conclusions

The decision to add a GC, within a strategy of combination therapy, to bring early RA under control still seems to divide rheumatologists. Doubts remain as to the best pretherapeutic work-up of patients and to their subsequent monitoring; also from the patients themselves, who may have preconceived negative opinions [170]. On the other hand, it should also be borne in mind that GCs are naturally produced endocrine hormones. So, while it may be imprudent to speak of a "safe" dose of exogenous GC, it is likely that at the lower end of the therapeutic GC exposition, there is a favourable benefit-risk ratio. The problem is to find the ideal dose, by disease state, since it is not the same for all individuals. There is an urgent need therefore to be able to test patients for GC sensitivity.

This clinical research topic is very large this review barely does justice to the knowledge base. The scope was given as GC therapy in rheumatic diseases and regrettably little other than RA was discussed because of space. We are getting close to the goal of being able to individualise therapeutic options and select optimal dose regimens, but still more refinement is needed in the tools available. At the present the following points seem pertinent:

- Early treatment and treat-to-target are important strategies in RA, and probably other systemic inflammatory diseases, resulting in improved patient outcomes.
- In RA, the option of a combination treatment with a fast-acting GC and a DMARD should be considered in most cases. Oral GC therapy, either at a stable low dose (≤7.5 mg/day) or an initial medium dose (~30 mg/day) that is rapidly tapered down, in combination with a traditional DMARD, (usually MTX) frequently results in rapid suppression of inflammation and can lead to clinical remission. It should be noted that monotherapy with GC is not advocated in RA.
- High oral GC doses (>30–100 mg prednisone equivalents/day) are associated with more adverse effects with a risk to bone loss in particular. When these are used over even short (≤3 months) durations there is a cumulative effect that considerably increases the probably of serious side effects (such as aseptic necrosis). In

MTX-resistant RA, recourse to a biologic DMARD seems to be more effective than GC pulse therapy.

- All GC preparations, given sufficient systemic bioavailability, will have measurable effects on the HPA axis and on bone metabolism, but these are dependent on dose, time of administration and duration of exposure. Low doses and relatively short durations of moderate doses are generally well tolerated and have a positive benefit/risk ratio. Depending on the indication intraarticular GC may be a suitable option.

- The fracture risk in patients and possibility BMD should be assessed and bone preserving agents prescribed accordingly. At a minimum, patient-specific calcium and vitamin D supplementation are advisable.

- GC's are effective adjuvants in the management in some other inflammatory rheumatic diseases such as lupus, vasculitis and giant-cell arteritis. These often require much higher GC exposure and the optimal therapeutic regimens are far from clear.

- More research is needed on the assessment of individual GC sensitivity, also on GC withdrawal and further optimisation of combination therapies.

**Compliance with ethical standards**

**Conflict of interest**  The author declares that they have no conflict of interest.

**Statement of human and animal rights**  All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and /or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Studies performed using animal tissues were done in accordance with accepted ethical standards.

**Informed consent**  Informed consent was obtained from all individual participants included in the study.

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